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INTERNAL MEDICINE

Asian Influenza A in Boston, 1957-1958
I. Observations in Thirty-Two Influenza-Associated Fatal Cases
Christopher M. Martin, Calvin M. Kunin, Leonard S. Gottlieb, Mildred W. Barnes, Chien Liu, and Maxwell Finland

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Bone Changes in Neurofibromatosis
Leslie J. Levene

Carcinoma of the Thyroid at Autopsy
Nathan Leonard Morgenstern and Yosef Leon Tiber

Serologic Response to Far East Influenza
Ion Gresser and Scott B. Halstead

Relationship Between Red Cell and Plasma Volume During Recovery from Pernicious Anemia
Ralph W. Massie

The Successful Medical Management of a Phytobezoar
David S. Dann, Sidney Rubin, Harold Passman, Manohar Deosaransingh, Anton Bauernfeind, and Max Berenbom

The Nephropathies of Sickle-Cell Disease
L. B. Berman and I. Tublin

Cystic Fibrosis of the Pancreas in a Young Adult
Robert G. Frazier and William J. Rowe

Recognition and Treatment of Hemopericardium and Hemorrhagic Pericarditis by Pericardiotomy
William J. Messinger and George E. Emmanuel

Syphilis
Herman Berman, Leslie Nicholas, Ira L. Schamberg, and Marvin S. Greenberg

Mechanisms of Urinary Concentration and Dilution
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TABLE OF CONTENTS

VOLUME 103 APRIL 1959 NUMBER 4

ORIGINAL ARTICLES

PAGE

Asian Influenza A in Boston, 1957-1958

I. Observations in Thirty-Two Influenza-Associated Fatal Cases
Christopher M. Martin, M.D.; Calvin M. Kunin, M.D.; Leonard S. Gottlieb, M.D.; Mildred W. Barnes, M.S.; Chien Liu, M.D., and Maxwell Finland, M.D., Boston .. 515

II. Severe Staphylococcal Pneumonia Complicating Influenza
Christopher M. Martin, M.D.; Calvin M. Kunin, M.D.; Leonard S. Gottlieb, M.D., and Maxwell Finland, M.D., Boston, with the Technical Assistance of Mildred W. Barnes, Clara Wilcox, and Ann Najarian 532

Augmentation
Embree H. Blackard, M.D., and Tinsley R. Harrison, M.D., Birmingham, Ala. 543

Serum Aldolase in Muscle Disease
Richard A. Thompson, M.D., and Paul J. Vignos Jr., M.D., Cleveland 551

Common Duct Stone Producing Charcot's Hepatic Fever Without Jaundice
Frank M. Howard Jr., M.D.; William J. Martin, M.D.; Maurice H. Stauffer, M.D., and George A. Hallenbeck, M.D., Rochester, Minn. 565

Bone Changes in Neurofibromatosis
Leslie J. Levene, M.B., B.S., Sunderland, England 570

Carcinoma of the Thyroid at Autopsy
Nathan Leonard Morgenstern, M.D., Oakland, Calif., and Yosef Leon Tiber, M.D., Los Angeles 581

Serologic Response to Far East Influenza
Capt. Ion Gresser (MC) and Capt. Scott B. Halstead (MC), U. S. Army (Res.) 590

Relationship Between Red Cell and Plasma Volume During Recovery from Pernicious Anemia
Ralph W. Massie, M.D., Nashville, Tenn. 593

The Successful Medical Management of a Phytobezoar
David S. Dann, M.D.; Sidney Rubin, M.D.; Harold Passman, M.D.; Manohar Deosaransingh, M.D.; Anton Bauernfeind, M.D., and Max Berenbom, Ph.D., Kansas City, Mo. 598

The Nephropathies of Sickle-Cell Disease
L. B. Berman, M.D., and I. Tublin, M.D., Washington, D. C. 602

Cystic Fibrosis of the Pancreas in a Young Adult
Robert G. Frazier, M.D., and William J. Rowe, M.D., Iowa City 607

Recognition and Treatment of Hemopericardium and Hemorrhagic Pericarditis by Pericardiotomy
William J. Messinger, M.D., Manhasset, L. I., N. Y., and George E. Emmanuel, M.D., New York 613

REVIEWS OF INTERNAL MEDICINE

Syphilis (Concluded)
Herman Berman, M.D.; Leslie Nicholas, M.D.; Ira L. Schamberg, M.D., and Marvin S. Greenberg, M.D., Philadelphia, with the Collaboration of T. Guthe, M.D., and C. J. Hackett, M.D., Geneva, Switzerland 621

CONTRIBUTIONS OF BASIC SCIENCE TO MODERN MEDICINE

Mechanisms of Urinary Concentration and Dilution
Ezra Lamdin, M.D., Boston 644

BOOKS

Reviews by Dr. William B. Bean and Others 672

REGULAR DEPARTMENTS

News and Comment 677

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VOLUME 103 APRIL 1959 NUMBER 4

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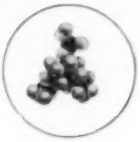

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc. **234**: 150, Aug. 1957.

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(b) If hyperglycemia or glycosuria persists develops, increase the daily dose from 500 g. to 625 mg. (2½ tablets of 250 mg.) with eakfast daily. In elderly patients, dosage ould be increased from 250 mg. according to tient response.

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1. Kirsner, J.B., et al.: M. Clin. North America *41*:499 (March) 1957.

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nutritive composition of average cereal serving

	Cereal, 1 oz. Whole Milk, 4 oz. Sugar, 1 teaspoon	Cereal** 1 oz.	Whole Milk 4 oz.	Sugar 1 teaspoon
CALORIES	203	104	83	16
PROTEIN	7.3 gm.	3.1 gm.	4.2 gm.	
FAT	5.3 gm.	0.6 gm.	4.7 gm.*	
CARBOHYDRATE	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
CALCIUM	0.169 gm.	0.025 gm.	0.144 gm.	
IRON	1.5 mg.	1.4 mg.	0.1 mg.	
VITAMIN A	195 I. U.	—	195 I. U.	
THIAMINE	0.16 mg.	0.12 mg.	0.04 mg.	
RIBOFLAVIN	0.25 mg.	0.04 mg.	0.21 mg.	
NIACIN	1.4 mg.	1.3 mg.	0.1 mg.	
ASCORBIC ACID	1.5 mg.	—	1.5 mg.	
CHOLESTEROL	16.4 mg.	0	16.4 mg.*	

*Nonfat (skim) milk, 4 oz., reduces the Fat value to 0.1 gm. and the Cholesterol value to 0.35 mg.
**Based on composite average of breakfast cereals on dry weight basis.

Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1958.

Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

Watt, B. K., and Merrill, A. L.: Composition of Foods-Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

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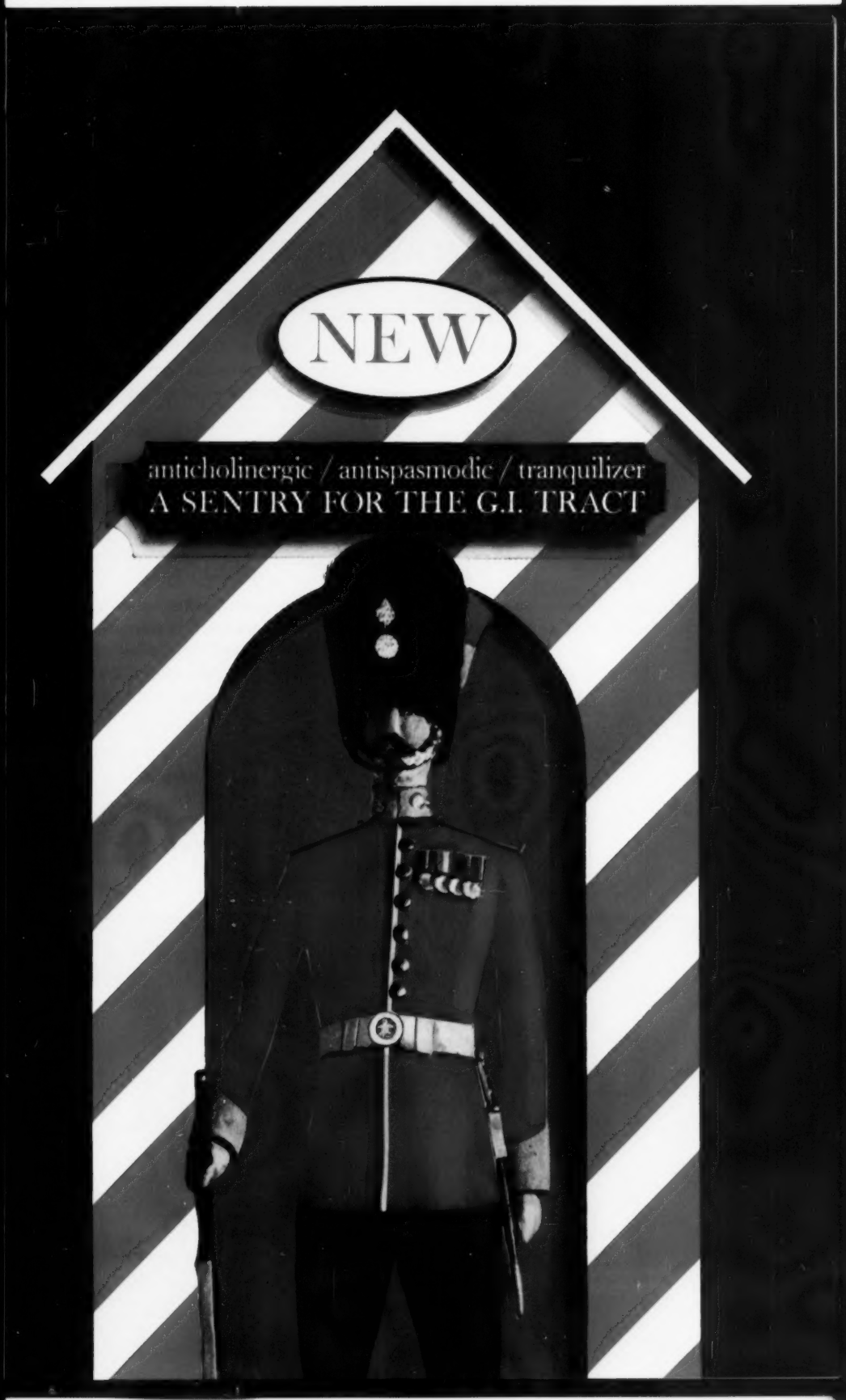
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References: **1.** McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, California, January 27, 1958. **2.** Strub, I. H., and Carballo, A.: To be published. **3.** Schuller, E.: Gaz. des Hôpitaux *10*:391 (Apr. 10) 1957. **4.** Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. **5.** La Barre, J.: Compt. rend. Soc. Biol. (Paris) *150*:1807 (Oct.) 1956. **6.** Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957. **7.** Data in Roerig Medical Department files.

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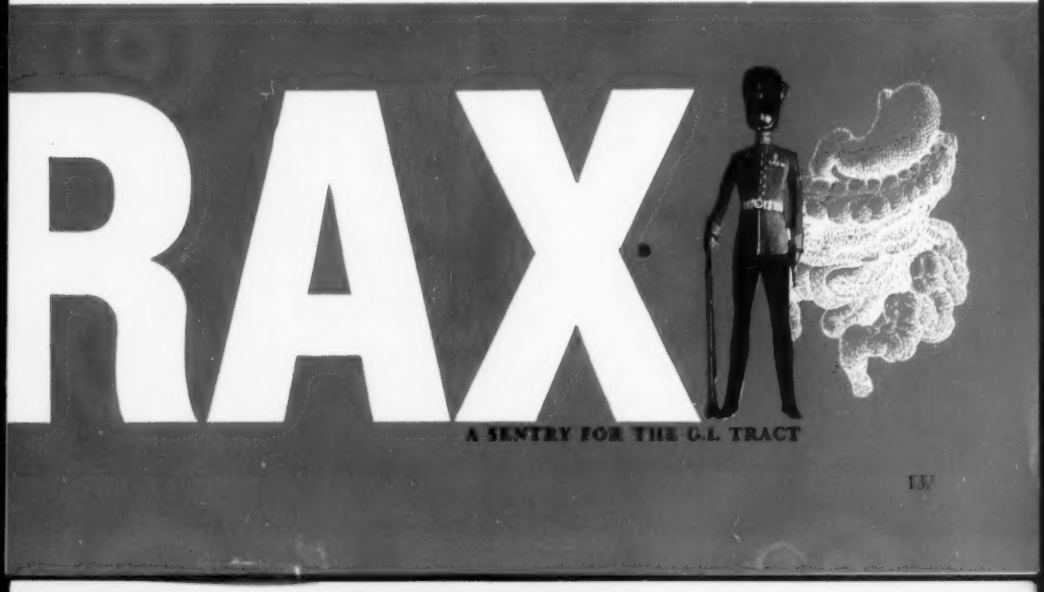

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Doshay, L. J., and Constable, K.: J.A.M.A. *163:* 1352 (Apr. 13) 1957.

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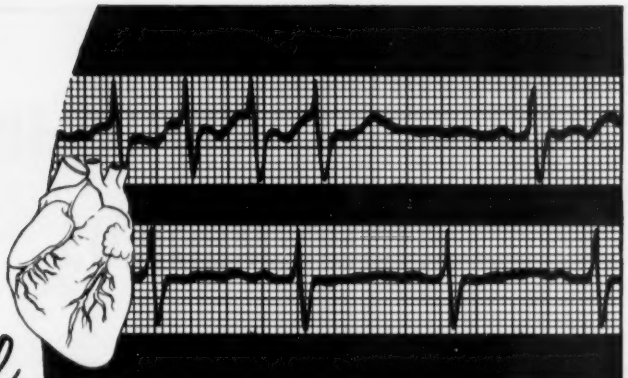

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Jordan and Grossman; Arch. Surg. 74: 871, 1957

Shingleton, et al; Surgery, 42: 12, 1957

Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956

Krane; Am. Pract. and Digest, 8: 1275, 1957

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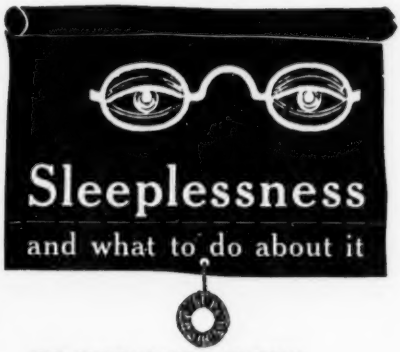

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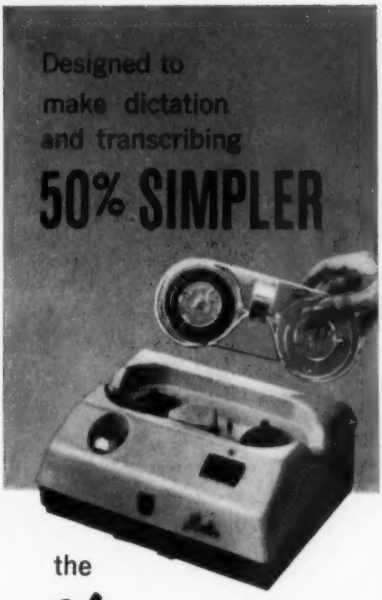

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A.M.A. ARCHIVES OF
INTERNAL MEDICINE

Asian Influenza A in Boston, 1957-1958

I. Observations in Thirty-Two Influenza-Associated Fatal Cases

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In the city of Boston, the pandemic of Asian influenza A was accompanied by an estimated 118 fatalities from influenza and pneumonia in excess of the norm—approximately 38 of them during the first wave in October and November, 1957, 42 in the second wave in March and April, 1958, and the remainder in the intervening months.* [1] The present report summarizes the pertinent clinical, pathological, virological, and bacteriological features in 32 influenza-associated deaths in the Boston area, with particular reference to problems of diagnosis and management.

Materials and Methods

Cases Studied.—A total of 43 fatal cases suspected of being influenza-associated were studied, but only 32 cases are reported here—23 of them from 11 Boston hospitals, 7 from 5 hospitals in suburbs and nearby towns, and 1 each from the Newport (R. I.) and Lawrence General (Mass.) Hospitals.† One fatality (Case 11) occurred in August; twenty-eight, during October and November; one (Case 9), late in December, 1957, and two (Cases 30 and 31), in March, 1958. In the 11 cases that were excluded, death was demonstrated to be due to causes other than influenza in 6 and specimens for study were inadequate in the other 5.

Criteria for Diagnosis of Influenza.—Each case was characterized by one or more of the following criteria: (1) isolation of Asian influenza A virus from antemortem throat washings or postmortem

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From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services and Mallory Institute of Pathology, Boston City Hospital; the Departments of Medicine and of Bacteriology and Immunology, Harvard Medical School; and the Departments of Pathology, Boston University School of Medicine and Tufts University School of Medicine. Senior Assistant Surgeon (R), Epidemic Intelligence Service, Communicable Diseases Center, United States Public Health Service (Dr. Kunin).

* Estimates of deaths for 1958 made from records of Division of Burial Permits furnished by Mr. William J. Kane, Chief of Vital Statistics, Boston Health Department.

† The hospitals and the names of the referring pathologists and internists are as follows: Boston City (Drs. Fernando Biguria, Robert C. Edmondson, A. Jane Lingeman, Armand Lozano, Stanislav Norkin, Lawrence J. Schneiderman, and Richard M. Zerkin), eight cases; St. Elizabeth's (Dr. James H. Graham), four; Faulkner (Dr. Philip M. LeCompte), Massachusetts Memorial (Drs. John Kelly, Richard H. Meade III, and Sheldon C. Sommers), Newton-Wellesley (Dr. David Skinner), and Winchester (Drs. James E. Fitzgerald and Robert Lennon), two each, and Boston Lying-in (Drs. Kurt Benirschke and Luke Gillespie), Boston State (Dr. Naomi Raskin), Boston V. A. (Dr. Caesar G. Tedeschi), Children's Medical Center (Dr. John M. Craig), Lawrence General (Dr. Leslie S. Jolliffe), Lemuel Shattuck (Drs. Thomas C. Chalmers, George W. Curtis, and Brian More), Milton (Dr. Philip M. LeCompte), Mount Auburn (Drs. David Hurwitz and Rocco Latorocca), New England Baptist (Dr. Eugene Perrin), Newport (Drs. William Freeman and Robert M. Webster), Peter Bent Brigham (Dr. Alvin Volkman), and Waltham (Dr. George G. Katsas), one each.

TABLE 1.—*Antecedent Disease in Thirty-Two Influenza-Associated Deaths* *

	No.
Heart Disease (rheumatic, 5; hypertensive, 4; coronary, 2; congenital, 1)	12
Pulmonary disease or respiratory insufficiency (bronchial asthma, 4; pulmonary fibrosis, chronic bronchitis, postoperative bronchogenic Ca, intrathoracic neurofibromata, multiple sclerosis, myasthenia gravis, 1 each)	10
Diabetes	2
Cirrhosis of liver	2
Pregnancy (4½, 5½, 6, 8½ mo.)	4
Miscellaneous (postlaparotomy, old nephrectomy for Ca of ureter, schizophrenia, obesity, 1 each)	4
None	8

* Eight patients had more than one antecedent disease; cf. Table 2.

TABLE 2.—*Certain Relevant Clinical Findings in Thirty-Two Influenza-Associated Deaths* *

Case	Sex	Age	Antecedent Disease	Days After Influenza Onset		Findings when Severe Disease First Recognized †						
				Pneumonia Began ‡	Died	Days After Influenza Onset	Blood Pressure	Pulse	Resp.	Rectal Temp., F	Rales	Consolidation	Pleural Fluid
A. Influenza Without Bacterial Complications													
1	F	47	Rheum. H. D.	None	2	2	110/70	88	24	101.5	Rl, Ll	0	0
2	M	44	Cirrhosis, diabetes, Hyp. H. D., obesity	1	2	1	226/160	120	28	104	Rl, Ll	Rl	0
3	M	60	Blood loss anemia, postlaparotomy	1	2	1	110/50 Shock	110	35	102	Rl, Ll	0	0
4	F	11	Neurofibromatosis	2	3	Dead on arrival at hospital							
5	F	30	Pregnant 8½ mo.	3	4	3	110/60	112	54	104	Lul	Lul	0
6¶	F	44	Rheum. H. D.	2	4	3	95/55 Shock	150	44	103.5	Rl, Ll	0	0
7	F	20	Pregnant 5½ mo.	3	4	3	110/60	140	48	104.5	Rl, Ll	Rl	0
8	M	38	Rheum. H. D.	None	4	2	140/80	115	20	104.5	0	0	0
9	F	15	Postnecrotic cirrhosis	2	4	3	90/40	120	48	100	Ll	Ll	0

tissues; (2) tracheal, pulmonary, or myocardial pathology consistent with that previously described for influenza; (3) in the absence of previous immunization, significant levels of hemagglutination-inhibiting antibody against influenza A/Japan 305/57 strain and/or of influenza A complement-fixing antibody; (4) specific staining with fluorescein-labeled Asian influenza A antiserum (see below). Cases 22, 24, and 25 were included although they did not meet the above criteria; each occurred at the height of the epidemic in the fall, presented classical clinical histories and findings of influenza at the onset of disease, and arose in families in which other cases of typical influenza were occurring. This series of cases, therefore, reflects selection on the basis of diagnostic features, hospital admission, and performance of a post-mortem examination; the series is also probably weighted with young adults.

Collection of Tissues.—Almost all tissues ‡ collected post mortem were placed in separate containers and within 12 hours divided into portions for virological, pathological, and fluorescent antibody studies; cultured on blood agar and chocolate agar plates and in blood broth, and frozen and stored in a solid carbon dioxide (Dry Ice) chest. A few specimens were received after one to four days of storage at refrigerator temperature or in a freezer at −20 C.

Virus Isolation.—Ten- or eleven-day embryonated hens' eggs were inoculated intra-amniotically for at least two passages with 20% tissue suspensions

‡ In most cases, trachea, lung, heart, liver, and spleen and in certain instances, hilar nodes, kidney, adrenal, brain, and bone marrow. Whenever possible, specimens of heart blood and of various body fluids were obtained for serological study.

							Shock						
10	F	52	Multiple sclerosis	2	4	2	120/80	110	35	102	Rl, Ll	0	0
11	M	15	None	3	5	3	120/70	180	>40	105.5	Rl	Rl	0
12	F	38	Rheum. H. D.	4	5	4	40/0	180	32	102	Rl, Ll	0	0
							Shock						
13	F	36	Pregnant 4½ mo.	5	7	6	118/70	>150	45	103.5	Rl, Ll	0	0
14	M	18	None	3	7	4	140/100	100	16	100.5	Rl, Ll	0	0
15	M	14	Cong. H. D.	None	9	1	120/80	136	44	101.5	0	0	0
						B. Postinfluenzal Staphylococcal Pneumonia							
16¶	F	15	None	2	3	3	100/60	>150	50	102	Rl, Ll	Rl, Ll	0
17	M	11	None	2	3	3	80/40	120	45	104	Rl, Ll	Rl, Ll	0
							Shock						
18	M	61	Bronchial asthma, cor. H. D., decomp.	3	4	3	140/72	110	40	101	Rl, Ll	0	0
19¶	F	19	None	3	6	5	70/36	140	28	104	Rl, Ll	0	0
							Shock						
20	F	41	Bronchial asthma	5	6	5	150/90	130	40	101	Rl, Ll	0	0
21	M	26	None	3	7	5	170/78	140	48	101.5	Rl, Ll	Rl, Ll	R+L
22	M	59	Rheum. H. D.; postpneumonectomy, rt., for Ca of lung	7	8	8	160/80	--	--	99.5	0	0	R
23	M	29	None	4	11	8	130/75	120	44	104	Rl, Lul	Ll	L
24	M	57	Chronic bronchitis	9	12	11	110/80	108	35	104.5	Ru, Lu	Ru	0
25	M	57	Bronchial asthma; cor. H. D., decomp.	12	13	11	Shock	>100	35	104	Lul	Lul	0
26	M	62	Hyp. H. D.; old myocardial infarct	12	17	13	210/90	94	30	103	Rml, Ll	Rl, Ll	0
						C. Postinfluenzal Bacterial Pneumonia, Nonstaphylococcal							
27	M	71	Hyp. H. D., decomp.; old nephrectomy for Ca of ureter	1	5	2	120/60	105	32	102	Rl, Ll	Rl	0
							Shock						
28	F	56	Pulmonary fibrosis; hyp. H. D.	2	5	2	170/120	74	55	103	Rl, Ll	Rl	0
29	F	36	Pregnant 6 mo.; myasthenia gravis	5	6	6	--	>100	>40	102	0	0	0
30	M	30	Diabetes	3	6	4	110/70	120	32	98	Rl, Ll	0	0
31	M	55	None	4	6	4	104/70	132	46	103	Rml	Rml	0
32	M	58	Schizophrenia	4	7	6	--	--	--	--	Ruml	Rl	R

TABLE 2.—*Certain Relevant Clinical Findings in Thirty-Two Influenza-Associated Deaths* *—Continued

					Findings when Severe Disease First Recognized †								
					Roentgenographic Findings								
Case	Sex	Age	Cyanosis	Notes	Mottled Densities	Consolidation	Pleural Fluid	Cavitation	Perihilar Congestion	Electrocardiogram	Leukocytes /Mm.³	Neutrophils, %	Corticosteroid Therapy
					A. Influenza Without Bacterial Complications								
1	F	47	Yes	§			Not done			--	7,900	85	No
2	M	44	Yes		Rl	0	0	0	0	LBBB, myocardial damage	8,500	79	No
3	M	60	Yes	‖	Ruml, Ll	Rl, Ll	0	0	++++	Left ventricular strain	--	--	No
4	F	11					Not done			--	--	--	No
5	F	30	Yes				Not done			--	7,100	98	Yes
6¶	F	44	Yes		Ru, Lu	0	0	0	0	Left ventricular strain	15,000	87	No
7	F	20	Yes				Not done			--	19,000	94	No
8	M	38	No		0	0	0	0	0	LBBB	9,200	78	No
9	F	15	Yes	#	Rml, Ll	Rml, Ll	0	0	0	--	8,000	75	No
10	F	52	No		0	0	0	0	+	Normal	13,000	85	No
11	M	15	Yes		Rl, Ll	Rl	R	0	0	--	18,000	88	No
12	F	38	Yes	**	Ll	Ll	0	0	0	Normal	--	--	No
13	F	36	Yes		Ruml, Lul	Rl, Ll	0	0	++	--	7,000	87	Yes
14	M	18	No	††	Ru, Ll	Rl, Ll	0	0	0	--	7,400	86	No
15	M	14	Yes	‡‡	0	0	0	0	++	Atrial fibrillation, premature vent. beats	13,000	70	No
					B. Postinfluenzal Staphylococcal Pneumonia								
16¶	F	15	Yes		Ruml, Ll	Rl, Lul	0	0	++	--	--	--	Yes
17	M	11	Yes		Rum	Rl, Lu	0	0	0	Auricular tachycardia	6,800	20	No
18	M	61	Yes		Ruml, Lul	0	0	0	+++	Normal	7,700	78	Yes
19¶	F	19	Yes	§§			Not done			Normal	4,800	59	No
20	F	41	No				Not done			--	16,000	86	No
21	M	26	Yes		Rl, Ll	Rl	0	0	++	--	5,500	4	Yes
22	M	59	No		0	0	R	0	+	--	15,000	72	No
23	M	29	Yes		Rl, Lul	Lul	L	Ll	0	Normal	7,400	63	Yes
24	M	57	Yes		0	Ru, Lu	0	0	0	Normal	20,000	64	Yes
25	M	57	Yes		Ll	Ll	R+L	0	+	--	--	--	Yes
26	M	62	Yes		Rml	0	R	0	++	Atrial & ventricular premature beats	9,300	82	No
					C. Postinfluenzal Bacterial Pneumonia, Nonstaphylococcal								
27	M	71	Yes	‖‖	0	Rl	R	0	++	Cor pulmonale; RBBB; atrial premature beats	19,000	86	No
28	F	56	Yes		Rl	0	0	0	++	Incomplete RBBB; ? acute anteroseptal infarction	11,000	--	No
29	F	36	Yes	¶¶			Not done			--	--	--	No
30	M	30	No		Ruml, Lul	Ll	0	0	+	--	24,000	73	No
31	M	55	Yes		Rl, Ll	Rl, Ll	0	0	+++	--	3,300	--	Yes
32	M	58	Yes				Not done			--	--	--	No

* M indicates male; F, female; H. D., heart disease; rheum., rheumatic; hyp., hypertensive; cor., coronary; cong., congenital; Ca, carcinoma; R, right; L, left; u, upper; m, middle; l, lower; 0, absent; +, slight; ++, moderate; +++, marked; ++++, maximal; ..., not recorded; BBB, bundle-bunch block.
† When physician was first consulted, or when attending physician first became aware of severe nature of illness.
‡ First appearance of hemoptysis, dyspnea, or pleuritic pain.
§ Morphine given 75 min. before death.
‖ Hemoglobin 8.5 gm/100 ml.
¶ Received monovalent Asian influenza vaccine, 200 CCA units subcutaneously: 16 days (Case 6), 23 and 6 days (Case 16), and 3 days (Case 19) before onset of influenza.
# Icterus, metabolic "liver flap," hemoglobin 8.8 gm/100 ml.
** Clinical diagnosis: acute abdomen.
†† Myoglobinuria.
‡‡ Atrial fibrillation began simultaneously with influenza; sudden death during second day of quinidine course.
§§ Scarlatiniform rash, diarrhea.
‖‖ Coma.
¶¶ Convulsion; on full doses of prostigmine and ambenonium chloride (Mytelase).

or 1:2 dilutions of tracheal secretions, as in previous studies.[3,8] Negative specimens were passed twice in monkey-kidney and HeLa-cell roller-tube cultures; hemadsorption tests with both chicken and guinea pig erythrocytes were performed on the 5th and 10th days after inoculation. The hemagglutinating viruses isolated were typed by standard techniques.

Serology. — Hemagglutination-inhibition (HI) studies with use of chicken erythrocytes were performed with the prototype A/Japan 305/57 strain,§ which had previously been passed in eggs, ferrets, and mice. Sera were pretreated with an equal volume of phosphate-buffered M/90 potassium periodate for 18 hours at 6-8 C, and the excess periodate then neutralized with an equal volume of 10% glycerin. Complement-fixation (CF) tests were performed with allantoic-fluid pools of the same strain and of influenza B, Lee strain, at dilutions of 1:2 and 1:8, respectively, with use of standard methods.[4]

With the methods used, none of over 75 preepidemic, prevaccine, or acute-phase sera (Days 1 to 3 of clinical influenza) from patients under 70 years of age contained levels of HI antibody higher than 1:5; and except in vaccinated persons, no preepidemic or acute phase sera contained CF antibody titers higher than 1:16.‖ HI titers of 1:10 and CF titers of 1:32 were, therefore, considered highly suggestive of recent infection or immunization, and 1:20 and 1:64, respectively, were considered diagnostic.

Pathology.—Tissues were fixed in 10% formalin and in Zenker's solution and stained with hematoxylin and eosin. Respiratory tract tissues were also stained by the Gram-Weigert method.

Fluorescent Antibody Staining.—Frozen sections of tissues were stained with fluorescein-labeled Influenza A/Malaya 311/57 strain # rabbit antiserum by methods similar to those previously described.[6] Before use as a histochemical stain, the solution of fluorescein-labeled antibody was absorbed once with ferret-liver powder and, to prevent nonspecific staining of leukocytes—particularly granulocytes—was absorbed once with an anion-exchange resin.* Specificity of the reaction was substantiated by (1) inhibition of staining by previous exposure of the tissue to unlabeled A/Mal 311/57 antiserum and (2) failure of labeled influenza B antiserum to stain the tissue or to inhibit subsequent staining with labeled A/Mal 311/57 antiserum.

§ Furnished by Dr. Keith E. Jensen.

‖ Of such sera, 85% had CF titers of 1:8 or less.

A strain of Asian influenza A closely related to A/Japan 305/57.[5]

* Dowex, 2 chloride (4% cross link, 20-50 mesh).

Results

Clinical Observations.—On the basis of ante- and postmortem bacteriologic studies (see below) the 32 patients studied were separated into three groups: (*a*) influenza without bacterial complication ("pure influenza"), 15 cases; (*b*) postinfluenzal staphylococcal pneumonia, 11 cases, and (*c*) postinfluenzal bacterial pneumonia, nonstaphylococcal, 6 cases.

Predisposing Disease.—Of the 32 patients, 21 had one or more chronic diseases of major proportions and 4 were pregnant women (Table 1). Twelve of the patients, including the three who died suddenly of nonpneumonic causes, had advanced heart disease; ten had either chronic intrinsic pulmonary disease or chronic respiratory insufficiency secondary to neurologic or neoplastic disease.

Sex.—There were 18 males and 14 females in the series; pregnant women accounted for the preponderance (9:6) of women in the pure influenza deaths. Males predominated in the groups with postinfluenzal bacterial pneumonia and among the patients with no antecedent disease (6:2).

TABLE 3.—*Comparison of Certain Clinical Features in Thirty-Two Influenza-Associated Deaths*

	Influenza Without Bacterial Complication	Postinfluenzal Staphylococcal Pneumonia	Postinfluenzal Bacterial Pneumonia Other than Staphylococcal
Cases, no.	15	11	6
Age, yr. *	11-60	11-62	30-71
	32	40	51
Sex, male/female	6/9	8/3	4/2
Days after onset influenza			
Pneumonia occurred *	1-5	2-12	1-5
	2.6	5.6	3.2
Death occurred *	2-7	3-17	5-7
	4.1	8.3	5.8
Interval, days, between time			
Onset of pneumonia & death *	1-4	1-7	1-3
	1.7	2.5	2.7
Severe disease first recognized & death *	0-3	0-4	0-3
	1.3 †	1.4	1.8
Asian influenza A vaccine >14 days before onset influenza	1	1	0
Findings when severe disease first recognized			
Severe hypotension	4/14	3/11	1/4
Pulse ≥ 120/min.	8/14	6/10	2/5
Respirations/min.			
31-40	3/14	4/10	2/5
>40	7/14	4/10	3/5
Temperature, rectal, F *	100-105.5	99.5-104.5	98-103
	103	102.5	101.5
No. lobes involved, mean			
Clinical — rales and/or consolidation	1.6	2.0	2.0
X-ray — mottled densities and/or consolidation	1.9	2.8	2.3
Cyanosis	11/14	9/11	5/6
Bilateral pulmonary involvement ‡	11/14	10/10	4/6
Pleural fluid ‡	1/14	5/11	2/6
X-ray findings of			
Cavitation	0/11	1/9	0/4
Perihilar congestion or pneumonia	4/11	6/9	4/4
ECG consistent with myocarditis	0/7	0/6	0/2
WBC, thousands/mm.³ *	7.0-19	4.8-20	3.3-24
	11	10	14
% neutrophils *	75-98	4-86	73-86
	86	59	80
Adrenal corticosteroid therapy	2/15	6/11	1/6

* Range/mean.
† Excluding Case 15.
‡ Clinically and/or by x-ray.

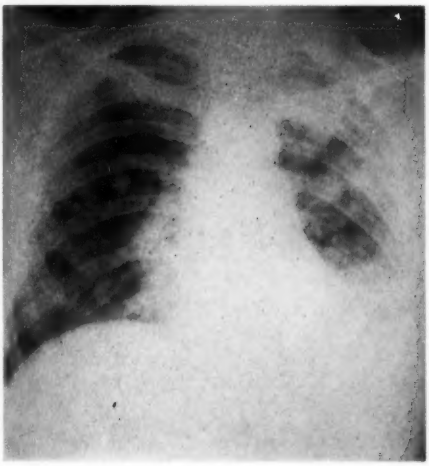
Age.—Fatalities from both influenza and postinfluenzal bacterial pneumonia occurred over a wide range of ages (11 to 71 years). Although the mean and median ages of the patients with pure influenza were somewhat lower than those of the patients with bacterial pneumonia (Table 3), these differences were not significant.

Clinical Features and Diagnosis.—The cases were characterized by a wide spectrum of modes of onset, symptoms and signs, laboratory findings, rates of progression, and modes of death (Table 2); however, the many common features permit a general description of a typical fatal course. The onset of the disease in patients who died of pure influenza was characterized by a 6- to 12-hour prodrome of malaise and fleeting myalgias, followed by the appearance of fever, chills, headache, severe myalgia, pain on ocular movement, nasal congestion, mild sore throat, and prostration. Between the second and third days of disease there developed dyspnea, hemoptysis, and pleuritic chest pain. Tachycardia, tachypnea, and cyanosis then rapidly ensued, with clinical findings of bilateral medium and coarse crepitant inspiratory rales usually involving two lobes, and with roentgenographic evidence of involvement of two to three lobes. Both the white blood cell count and the percentage of polymorphonuclear neutrophils were usually either within normal limits or slightly elevated. The subsequent course was marked by rapid worsening of respiratory function, intensification of the cyanosis, frothy hemoptysis, and, terminally, shock and signs resembling those of pulmonary edema. Death most commonly occurred about the fourth day after onset of influenza, 24 to 48 hours after the onset of pneumonia, or 12 to 36 hours after severe disease was first clinically recognized.

Both the general course and the findings in patients with fatal postinfluenzal bacterial pneumonia were virtually identical to those in patients with pure influenza (Table 3). Among the differences were a somewhat later onset of symptoms of pneumonia (third to fifth days or later after onset of influenza) and a somewhat longer interval between the time of onset of pneumonia and the time of death (24 to 72 hours) among those with bacterial infection; neither of these differences was statistically significant. Demonstrable pleural fluid at the time severe disease was first recognized was significantly commoner ($0.05>P>0.01$) in the patients with bacterial pneumonia; this difference was blurred, however, by the eventual appearance of pleural fluid in 4 of the 15 cases of pure influenza. Effective distinction between staphylococcal or other bacterial pneumonia and pure influenza with pulmonary involvement—in time to initiate specific chemotherapy—rested solely on Gram-stain demonstration of pathogens in the sputum (6 of 7 sputum specimens examined in the 17 cases of bacterial pneumonia) or in the pleural fluid (the single effusion studied of the 10 that were demonstrated ante mortem in the 17 cases) or on roentgenographic findings of cavitation (1 in 13 of the cases of bacterial pneumonia examined radiologically).

Roentgenographic Findings.—The marked variability in roentgenographic

Fig. 1 (Case 23).—Staphylococcal pneumonia. Posteroanterior view, eight days after onset of influenza, showing areas of consolidation and mottled densities in left upper and lower and right lower lobes, fluid in left pleural cavity, and cavitation in left lower lobe.



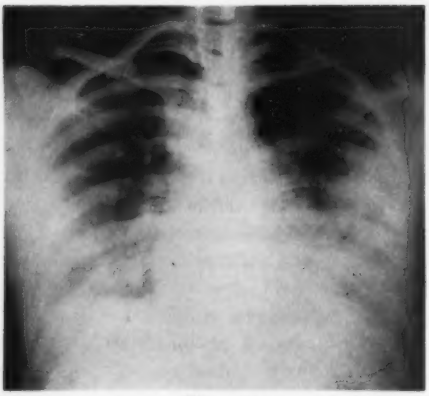


Figure 2

Fig. 2 (Case 13).—Influenza without bacterial complication. Anteroposterior portable view, six days after onset, showing partial consolidation of both lower lobes, mottled densities in all five lobes, and perihilar congestion (+).

Figure 3

Fig. 3 (Case 31).—Pneumococcal pneumonia. Anteroposterior portable view, four days after onset of influenza, with partial consolidation and mottled densities in both lower lobes and perihilar congestion (+++).

findings at the time severe disease was first recognized is suggested in Table 2 and illustrated in Figures 1 to 6. Except when cavitation was demonstrable, the cases of pure influenza with pulmonary involvement and of postinfluenzal bacterial pneumonia were often radiologically indistinguishable, and both—particularly the latter—were easily confused with uncomplicated pulmonary edema or congestion.

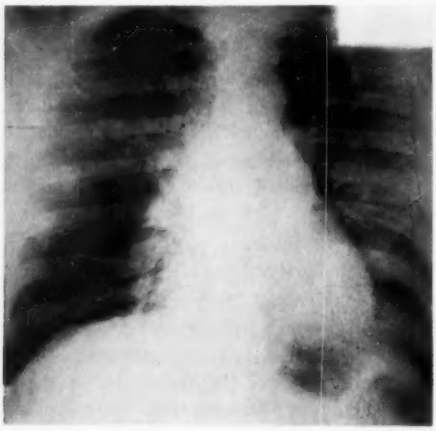
Myocarditis.—In Case 11, the only patient with striking pathologic findings of myocarditis, the diagnosis was not suspected ante mortem and an electrocardiogram was

Fig. 4 (Case 3).—Influenza without bacterial complication. Anteroposterior portable view, two days after onset, with consolidation in both lower lobes, mottled densities throughout right lung and in left lower lobe, and perihilar congestion (++++).

Figure 4

Fig. 5 (Case 18).—Staphylococcal pneumonia. Anteroposterior portable view, three days after onset of influenza, showing mottled densities in all five lobes and perihilar congestion (+++).

Figure 5



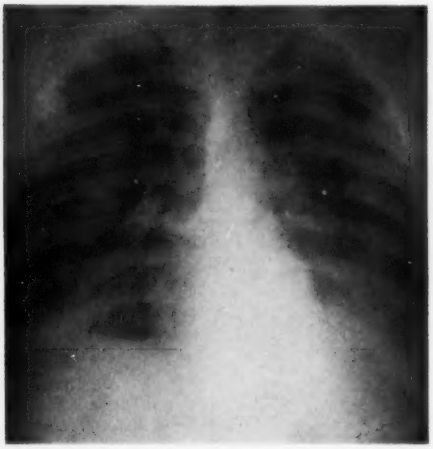


Fig. 6 (Case 30).—Pneumococcal pneumonia. Posteroanterior view, four days after onset of influenza, showing partial consolidation of left lower lobe, mottled densities in all five lobes, and perihilar congestion (+).

not taken; no signs of myocarditis—other than tachycardia—were noted in this case. An erroneous clinical diagnosis of myocarditis was made in one case of staphylococcal pneumonia (Case 19), based on findings of chest pain, shock, tachycardia, and a proto-diastolic gallop.

Pregnant Women.—In four women who died during pregnancy, gestation had advanced four and one-half, five and one-half, six, and eight and one-half months, respectively. Labor began in Case 7 (five and one-half months) on the fourth day after onset of influenza; the patient delivered a stillborn fetus and died 12 hours later. The time of death of the fetus in Case 29 (six months) is not known; the fetus was active, and fetal heart sounds were of normal rate and quality six hours before the patient died. In each of the other two cases, intrauterine fetal death occurred shortly before the deaths of the mothers.

Duration of Disease.—The downhill course in patients who died of pure influenza was more rapid than that in patients with postinfluenzal bacterial pneumonia. The mean interval between the time of onset of pneumonia, as judged from the first appearance of hemoptysis, dyspnea, or pleuritic chest pain, and the time of death in the cases of fatal pure influenza was 1.7 days; for the staphylococcal and other bacterial pneumonias, the intervals were 2.5 and 2.7 days, respectively (Table 3). The mean intervals between the time when severe disease was first recognized and the time when death occurred in the three groups were 1.3 (pure influenza), 1.4 (staphylococcal pneumonia), and 1.8 days (other bacterial pneumonia).

Management.†—Virtually all the fatal cases received vigorous supportive therapy in the form of oxygen and atmospheric humidification, and, when hypotension ensued, pressor amines. Many were treated for pulmonary edema with morphine, aminophylline, tourniquets applied to the extremities, and rapid digitalization. A number received bronchodilator drugs and/or Alevaire (alkylaryl polyether alcohol detergent) by inhalation, and in one or two cases, positive-pressure oxygen therapy, tracheotomy, transfusions, or pooled human γ-globulin were used. There was no clear evidence that any of these maneuvers —except, perhaps, oxygen therapy—significantly altered the course of the disease.

Various corticosteroids, in doses approximating 200 to 400 mg. of hydrocortisone per day, were administered in 9 of the 32 cases. A comparison of the six cases of staphylococcal pneumonia in which adrenocortical steroids were used with the five in which they were not—two groups roughly similar as to age, sex, and severity of the disease (Table 2)—reveals a mean interval between the times of onset of pneumonia and of death of 2.8 ± 2.4 days in the steroid-treated and of 2.2 ± 1.8 days in the non-steroid-treated; this difference is not significant. Similarly, the interval between the times when severe disease was first recognized and when death occurred was 1.5 ± 1.0 days in the steroid-treated and 1.2 ± 1.6 days in the non-steroid-treated.

Mode of Death.—In the majority of patients, death appeared to be due to asphyxia.

† Antibiotic therapy is discussed in the second paper in this series.[7]

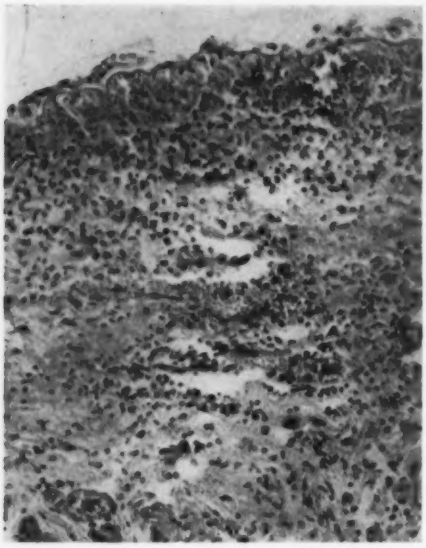


Fig. 7 (Case 8).—Trachea (virus-positive). Necrotizing tracheitis (+++). Necrotic, desquamating epithelium, and submucosal edema, hyperemia, and infiltration by neutrophils and mononuclear cells; × 200.

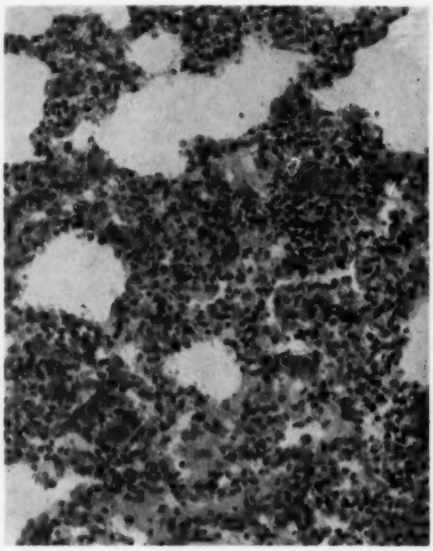


Fig. 8 (Case 4).—Lung (virus-positive). Interstitial pneumonitis (++++) and intra-alveolar edema (++). Edema and mononuclear-cell infiltration of the interstitium; × 200.

Fig. 9 (Case 13).—Lung (virus-positive). Hyaline membrane (+++), interstitial pneumonitis (+), intra-alveolar hemorrhage and edema (+), dilated blood vessels, ruptured alveoli, and intra-alveolar mononuclear exudate; × 200.

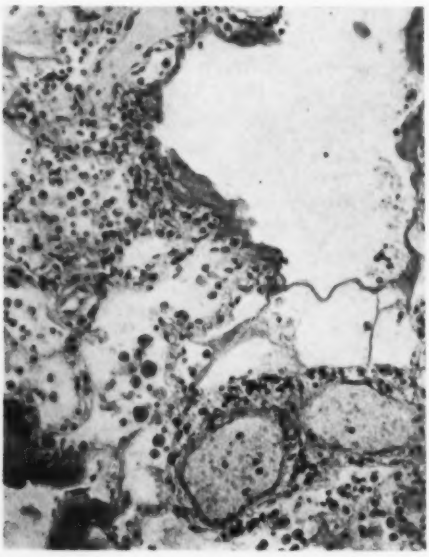
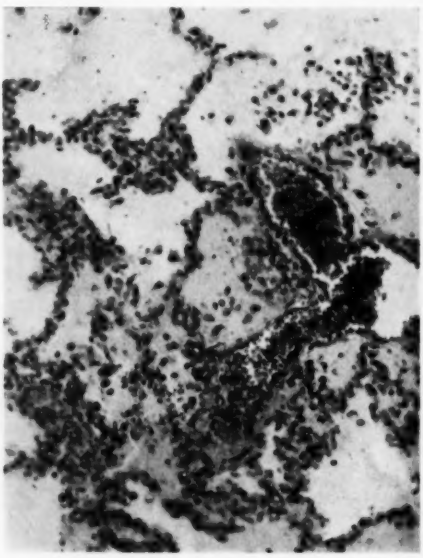


Fig. 10 (Case 10).—Lung (virus-positive). Intra-alveolar edema (+++), interstitial pneumonitis (++), and intra-alveolar mononuclear exudate; × 200.



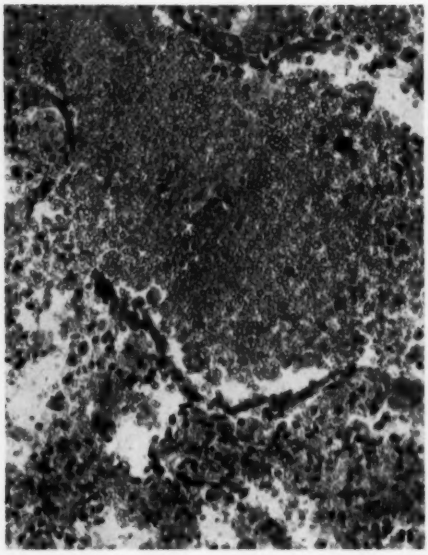


Fig. 11 (Case 6).—Lung (virus-negative). Intra-alveolar hemorrhage (++++) and ruptured alveoli; × 200.

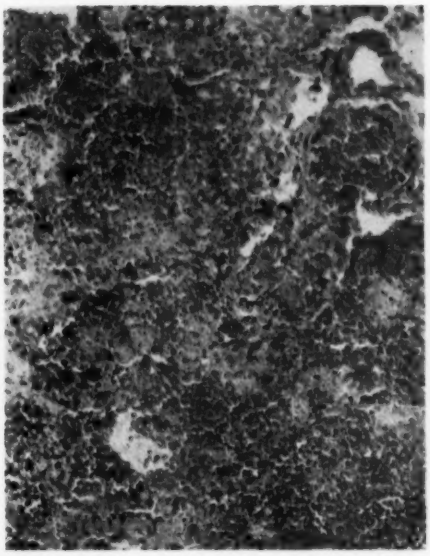


Fig. 12 (Case 17).—Lung (virus-positive). Necrotizing pneumonia (++++). Necrosis of alveolar walls, hemorrhage, and degenerated leukocytic infiltrate; × 200.

Fig. 13 (Case 11).—Heart (virus-negative). Interstitial myocarditis (+++). Edema and necrosis of muscle fibers and interstitial edema and infiltration by mononuclear cells, scattered lymphocytes and plasma cells, and occasional neutrophils; × 200.

Fig. 14 (Case 22).—Heart (virus-negative). Focal acute myocarditis (+). Slight fragmentation of myocardial fibers and focal infiltration of neutrophils and mononuclear cells—question influenzal; × 450.

In the seven patients with staphylococcal pneumonia who did not receive specific chemotherapy, the relative roles of asphyxia and sepsis are difficult to define. The three sudden, nonpneumonic deaths in cardiac patients (Cases 1, 8, and 15)—none of which is satisfactorily explicable pathologically—are presumed to have involved fatal arrhythmias.

Pathology.—Gross and microscopic pathological findings in this series (Table 4, Figs. 7 to 14) closely approximated those described in fatal cases due to earlier strains of influenza A [8,9] and to influenza B.[9,10] The most striking general feature was the marked variation in the findings, not only from case to case but from one portion of lung to another in the same case. In addition, no particular pattern of lesions could be correlated with a given day of influenza or of postinfluenzal bacterial disease.

The commonest finding in all groups was intra-alveolar hemorrhage and/or edema (28 cases) and in the patients with pure influenza, interstitial pneumonitis (13 cases). Somewhat less common in fatal pure influenza were hyaline membrane formation and tracheitis, each observed in nine cases. Multiple thromboses in pulmonary vessels, a finding previously reported in other cases,[8] were not seen frequently in the series.

Staphylococcal pneumonia was characterized in 9 of 10 cases by uniformly severe, necrotizing pneumonia, and associated bronchopneumonia; in the 10th there was minimal pneumonia with severe necrotizing tracheobronchitis, a finding also noted in 5 other cases.

In the single case of severe, diffuse interstitial myocarditis (Case 11), there was marked necrosis of muscle fibers and a cellular infiltrate of mononuclear cells, lymphocytes, a few plasma cells, and occasional neutrophils (Fig. 13). In addition, focal interstitial myocarditis of low degree and questionable significance (Fig. 14) was present in nine cases.

The fetuses and placentas from Cases 7, 13, and 29 were studied. The fetuses showed principally diffuse petechiae in parenchymal organs and scattered thromboses—findings consistent with the effects of anoxia; only one (Case 7, five and one-half months) showed a mild monocytic infiltration of the pulmonary interstitium. Each of the placentas contained foci of nonspecific intervillous thrombosis and hemorrhage.

Bacteriology.—No unusual pathogens were isolated from postmortem specimens; Hemophilus influenzae was conspicuously absent. The lungs of patients with pure influenza yielded either no growth (eight cases) or only a few organisms not ordinarily considered respiratory pathogens (Table 4). From none of these patients had pathogens been isolated during life. All the cases of staphylococcal pneumonia yielded strains of Staphylococcus pyogenes var. aureus in large numbers. In the third group, only a few nonpathogens were cultured from the lungs of Cases 27, 30, and 31; in each of these cases, the sputum obtained during life had yielded Diplococcus pneumoniae (pneumococci) and the patient had received penicillin. Pure cultures of Streptococcus hemolyticus and of D. pneumoniae Type 3 were obtained in Cases 29 and 32, respectively. The bacteriologic findings in the virus-positive Case 28 are equivocal; sputum cultures during life yielded no bacterial pathogens. Post mortem, the clinically uninvolved left lower lobe was sterile, but the consolidated right lower lobe yielded large numbers of Proteus vulgaris and a few colonies of coagulase-positive hemolytic S. pyogenes var. aureus.

Virology.—Asian influenza A was the only virus demonstrated in the fatal cases; 15 strains were isolated from tissues of 14 (44%) of the cases, death in some of them having occurred as late as the seventh day after onset of influenza. In a 15th case isolation of a virus (Case 11, lung) was reported by another laboratory, but this was lost in subsequent passage, and attempts at

TABLE 4.—*Certain Relevant Postmortem Findings in Thirty-Two Influenza-Associated Fatal Cases* *

Case	Onset Influenza to Death, Days	Necrotizing Tracheo-bronchitis	Lungs						
			Hyaline Membrane	Interstitial Pneumonitis	Intra-Alveolar		Thromboses Small Vessels	Necrotizing Pneumonia	Broncho-pneumonia
					Hemorrhage	Edema			
A. Influenza Without Bacterial Complication									
1	2	±	0	+	0	0	0	0	0
2	2	++	+	++	+	++++	0	0	++
3	2	++	+++	+++	0	++++	0	0	++
4	3	0	+++	++++	++	++	0	0	+
5	4	+	++	+	0	+++	0	0	+
6	4	+++	++++	+	++++	++	0	0	+
7	4	No postmortem examination							
8	4	+++	0	0	++	+	0	0	+
9	4	0	+++	++	+	++++	0	+	+++
10	4		0	++	0	++	0	0	+
11	5	+	++++	+	0	+	0	0	0
12	5	+++	+++	+++	+	++	0	0	+
13	7	+	+++	+++	+	++	0	0	0
14	7	0	0	+	+	++	0	0	+
15	9	+	0	+	0	0	0	0	0
B. Postinfluenzal Staphylococcal Pneumonia									
16	3	++++	+	0	++++	+++	0	++	+++
17	3	+++	0	0	+	+++	0	+++	+
18	4	+++	0	+	++++	++++	0	++++	++++
19	6	++++	0	+++	++	++	0	++	++
20	6		0	0	+	++	0	++++	++++
21	7	+++	0	0	+	++++	0	+++	+++
22	8	++++	0	+	+++	++	0	+	+
23	11	No postmortem examination							
24	12		±	0	++	++	0	++++	++++
25	13	0	0	0	++++	+++	++ Septic	++++	+++
26	17		0	0	+	++	0	++++	++++
C. Postinfluenzal Bacterial Pneumonia, Nonstaphylococcal									
27	5		0	++++	0	+++	0	0	+++
28	5	0	0	0	0	+++	0	+	++
29	6	+++	0	0	0	++	0	0	+
30	6		+++	++	+++	0	0	0	+++
31	6	0	++++	0	++++	+++	0	Lobar, lobular pneum., with foci of necrosis	
32	7	Bronchitis	0	0	0	++	++ Septic	0	++

TABLE 4.—*Certain Relevant Postmortem Findings in Thirty-Two Influenza-Associated Fatal Cases* *—Continued

Case	Myocarditis	Other Influenza-Related Pathology	Other Pathology	Postmortem Bacteriology	Asian Influenza A Virus Isolation	Postmortem Serology †		Tissues Showing Specific Fluorescence
						C. F.	H. I.	
			A. Influenza Without Bacterial Complication					
1	0	0	RHD; Parker-Weiss syndrome [1]	L—no growth	Pos (L, Ts) Neg (H)	<8	<5	Lung; heart ±
2	+	0	Fatty nutritional cirrhosis	L—no growth	Pos (L)	8	5	Lung
3	+	Adenitis; loss spleen follicles	Postlaparotomy	L—no growth	Neg (L, H)			
4	0	Adenitis	Neurofibromatosis	L—no growth	Pos (Ts) Neg (S)	<8	5	Lung, trachea; spleen ±
5	+	0	RHD	L—no growth	Neg (L, H)			
6	0	Acute splenitis	RHD; Parker-Weiss syndrome [1]	L—no growth	Neg (L)			
7	No postmortem examination							
8	0	0	RHD; congestive failure	L—rare α-strep.	Pos (Sp)	<8	5	
9	0	Adenitis	Postnecrotic cirrhosis, splenomegaly	L—rare Candida sp.	Pos (TW)	<8	5	
10	0	0	Emphysema	L—rare coliform sp.	Neg (L)	A. C.	<5	
11	++++	0	0	L—rare Proteus	Pos (L)			
12	+	0	RHD	L—no growth	? Pos (L) ‡ Neg (L, H, Ts)	<8	<5	Trachea
13	0	0	0	L—few Candida sp.	Neg (L, H)			
14	+	0	Myoglobinuric kidneys	L—few α-strep.	Pos (Ts)	<8	<5	Trachea
15	0	0	Cong. HD, cardiac cirrhosis	L—no growth	Neg (L, H)			Trachea
					Neg (L)	64	5	
			B. Postinfluenzal Staphylococcal Pneumonia					
16	0	0	0	L—Staph. aureus	Neg (L)	128	20	
17	0	Myeloid hyperplasia, adenitis	Cerebral edema	L—Staph. aureus, Strep. hem.	Pos (Ts)	<8	<5	Lung, trachea
18	0	Adenitis	Chest only	L—Staph. aureus	Pos (Ts) Neg (S)	16	5	
19	0	Splenitis, adenitis	Focal interstitial nephritis; meningitis	L, H, CSF—Staph. aureus	Neg (Ts)	32	<5	Spleen ±
20	0	0	Emphysema	L, Lv, Emp—Staph. aureus	Pos (L)	16	<5	
21	0	0	0	L—Staph. aureus	Neg (TW)	64	5	Lung
22	+	0	RHD, Ca of lung, postpneumonectomy	L, T, Hb—Staph. aureus	Neg (H) §			
23	No postmortem examination							
24	0	0	ASHD	L—Staph. aureus	Neg (Sp) Neg (L) §	8 ‖	10 ‖	
25	+	Adenitis	Chest only	L—Staph. aureus	Neg (T) §			
26	0	0	Myocardial fibrosis	L—Staph. aureus	Neg (L)	128	40	

C. Postinfluenzal Bacterial Pneumonia, Nonstaphylococcal

27	+	0	Hyper. HD; remote nephrectomy	L—Proteus, few Staph. aureus	Neg (L, H)	64	QNS	
28	0	0	Hyper. HD	L—Proteus, few Staph. aureus	Pos (Ts)			
29	+	0	Myasthenia gravis	L—Strep. hem.	Neg (L, H, S)	32	<5	Spleen ±
30	0	0	Diabetes mellitus	L—few enterococci, A. aerogenes	Pos (Ts)			
31	0	Adenitis, splenitis	0	L—few Candida sp.	Pos (L)	64	<5	Lung
32	0	0	0	Emp—pneumococcus, Type 3	Pos (T, N)	32	10	Lung

• CSF indicates cerebrospinal fluid; Emp, empyema; H, heart; Hb, heart blood; L, lung; Lv, liver; N, hilar node; Neg, negative; Pos, positive; S, spleen; Sp, sputum, ante mortem; T, trachea; Ts, postmortem tracheal secretions; TW, throat washings, ante mortem; RHD, rheumatic heart disease; Hyper HD, hypertensive heart disease; Cong. HD, congenital heart disease; ASHD, arteriosclerotic heart disease; 0, absent; ±, equivocal; +, slight; ++, moderate; +++, marked; ++++, severest.

† Reciprocal of titer (initial serum dilution).

‡ Positive in another laboratory, negative in this laboratory.

§ Diagnosis of influenza based on clinical course, epidemiology.

‖ 3 days ante mortem.

isolation were unsuccessful in this laboratory.

Influenza virus could not be isolated from any of the nine hearts that showed minimal myocarditis, and inoculations in chick embryos, various tissue cultures, and suckling mice of the heart that showed severe myocarditis (Case 11) failed to yield any recognizable virus. Tissues from the three fetuses were all negative for influenza virus.

Serology.—Levels of CF and HI antibody of probable significance were demonstrated at autopsy as early as the fifth and seventh days, respectively, after onset of influenza. CF antibody was demonstrable in available body fluids in one of nine cases of pure influenza, in four of eight cases of staphylococcal pneumonia, and in all of four cases of other bacterial pneumonia. HI antibody was demonstrated in the fluids in none, three, and one of the same groups of cases, respectively.

Demonstration of Virus in Tissues by Fluorescent Antibody Staining.—With the methods used, specific fluorescence, indicating the presence of immunologically intact viral antigen, was demonstrated unequivocally in only one cell type—the interstitial macrophage—in both nucleus and cytoplasm. Viral antigen was not demonstrable in the few tracheal or bronchial epithelial cells still intact, in alveolar cells, or in fibroblasts, neutrophils, or lymphocytes, and none was detected lying free in the alveoli or in tissue spaces. Fluorescence-positive macrophages were observed in the submucosa of 5 of 19 tracheas and in the interstitium and alveolar exudate of 7 of 29 lungs. Viral antigen in trachea or lung or both was demonstrated in 7 of the 14 virus-positive cases and in 3 of the 18 virus-negative cases (Table 4); antigen was detectable as late as the seventh day after onset of influenza.

One of the 28 hearts studied (Case 1, no myocarditis) revealed the presence of influenzal antigen; a cluster of fluorescent macrophages was seen surrounding an arteriole and extending a short distance into

the interstitium. Because fluorescence was seen in this heart only in sections from one tissue block and was absent in sections from four other sites, the observation must be considered of equivocal significance. No influenzal antigen was detectable in multiple sections of the heart showing severe diffuse myocarditis (Case 11).

The presence of occasional dimly fluorescent macrophages in 3 of 10 spleens studied was also considered of equivocal significance, particularly since virus could not be isolated from any of them. Fluorescent macrophages were not seen in any of the 16 livers, the 3 fetuses and placentas, or the few hilar nodes, kidneys, and miscellaneous tissues examined.

Comment

Analysis of these 32 cases reemphasizes several known facts concerning severe influenza and its complications, suggests the importance of some revisions in current approaches to the severe disease and its management, and underlines the pressing need for improved facilities for management of acute respiratory insufficiency.

The data in this series confirm preepidemic predictions by public health authorities,[12,13] based on experience in previous epidemics: 1. Major population groups particularly susceptible to severe disease (and therefore prime candidates for immunization) were pregnant women and those with chronic heart disease and chronic respiratory insufficiency. 2. Influenzal and postinfluenzal pneumonias were the commonest and severest complications. 3. Myocarditis was infrequent and generally minimal. 4. The occurrence of hemoptysis, tachypnea, and cyanosis in influenza—with or without prominent pulmonary findings—is highly indicative of potentially fatal disease. 5. Bacterial—particularly staphylococcal—pneumonia, when it occurs in adults following influenza, is generally severer and more rapidly progressive than it is under other circumstances.

On the basis of experience with a wide variety of infectious diseases, most authorities have consistently opposed the hasty administration of antibiotics prior to the effective clinical—or, preferably, bacteriologic—demonstration of a specific pathogen and have particularly decried the indiscriminate use of antibiotics in insusceptible virus infections.[14] Implicit in these sound principles is the tacit assumption that there is enough time to make an accurate diagnosis.

In the instance of severe influenza, as seen in the three groups studied (Tables 2 and 3), the interval between the time when severe disease was first recognized and the time when death occurred was 48 hours or less in 25 (81%) of 31 cases. Moreover, in a considerable proportion of cases of severe influenza the bacteriologic, radiographic, and other laboratory techniques used were not effective in distinguishing between pure influenza and postinfluenzal bacterial pneumonia rapidly enough to be useful; the opportunity for successful specific treatment was therefore probably missed in some of the cases of bacterial pneumonia.[7]

One is forced to the conclusion that in times of epidemic influenza, in localities in which major staphylococcal infections are known to be common, all cases presenting with signs of severe, potentially fatal influenza should be diagnosed and treated promptly as bacterial pneumonias—probably staphylococcal—until the diagnosis is proven otherwise. On the other hand, the data in this series lend no support to the practice of using "prophylactic" antibiotics in uncomplicated influenza; indeed, as shown in the second paper of this series, they contradict it.[7]

The relative futility of standard, vigorous supportive measures in preventing eventual asphyxia in the cases reported underscored the need both for a better understanding of pathogenetic mechanisms in fatal influenza and for a practical device which will function as an "artificial lung"—capable of efficient extrapulmonary gaseous exchange of oxygen and carbon dioxide—during periods of acute respiratory insuffi-

ciency. Such an apparatus is undergoing development in several laboratories.[15]

Although the data in the present series suggest that the administration of corticosteroids does not significantly alter the course of fatal influenza, the cases are too few in number and the controls inadequate to state this point with assurance.

Summary

Studies of 32 Asian influenza A-associated fatalities in Boston and environs, in patients aged 11 to 71, reveal a spectrum of clinical courses, laboratory findings, and postmortem findings not unlike those associated with fatal cases during earlier influenza epidemics. Among the cases were a high percentage with antecedent heart disease or pulmonary insufficiency.

Strains of Asian influenza A virus were isolated from tissues of 44% of the cases and, by means of fluorescein-labeled antibody techniques, influenza A viral antigen was demonstrated in interstitial macrophages of respiratory tract tissues in 31%.

Except when Gram-stain studies of sputum revealed specific pathogens or when roentgenographic studies demonstrated pulmonary cavitation, it was not possible to make a prompt diagnostic differentiation between pure influenzal pneumonia and postinfluenzal bacterial pneumonia.

It is suggested that in times of epidemic influenza, and in areas where staphylococcal infections are highly prevalent, cases presenting with the signs usually associated with fatal influenza should be treated promptly as bacterial—particularly staphylococcal—pneumonias, unless or until that diagnosis is disproved.

The need for a practical "artificial lung" to support patients in the acute respiratory insufficiency of severe influenza is emphasized.

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Asian Influenza A in Boston, 1957-1958

II. Severe Staphylococcal Pneumonia Complicating Influenza

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With the technical assistance of Mildred W. Barnes, Clare Wilcox, and Ann Najarian

Prior to the 1957-1958 epidemic of Asian influenza A, public health authorities in the United States warned that a high incidence of postinfluenzal staphylococcal pneumonia could be anticipated, and they widely publicized recommendations for limiting the severity of this complication.[1,2] In virtually all sections of the nation many cases of staphylococcal pneumonia did indeed occur; available data indicate that despite the forewarning the Staphylococcus accounted for the largest single group of fatalities due to postinfluenzal bacterial pneumonia.[3]

The purpose of the present report is to present and compare the findings, clinical course, and management in 11 fatal cases and 9 nonfatal cases of post-Asian-influenzal staphylococcal pneumonia occurring in Boston and environs; to analyze the properties of the strains of staphylococci responsible, and to demonstrate the importance of the rapid choice of effective antistaphylococcal chemotherapeutic agents.

Materials and Methods

Human Cases.—All the cases studied occurred in the months of peak incidence of influenza in Boston, namely, October and November, 1957, and March, 1958. The 11 fatal cases here reported were among those included in a previous paper.* Six additional fatal cases of staphylococcal pneumonia were studied, but no clear clinical, virological, or pathological evidence of previous influenza viral infection was adduced in them, and they are not included. In addition, 23 cases of severe but nonfatal staphylococcal pneumonia were encountered and studied. Antecedent infection with Asian influenza A virus was demonstrated in nine, and only these are here reported. Influenza was ruled out in 10 cases; in the remaining 4, although almost certainly postinfluenzal, specimens were inadequate for serological diagnosis. The 11 fatal cases reported occurred at eight hospitals†; all the nonfatal cases, at the Boston City Hospital.

Diagnosis of Influenza.—The criteria for diagnosis of influenza in the fatal cases, as well as the virological, serological, and pathological methods employed, have been previously described.[4] Serological evidence in the nonfatal cases interpreted as indicating recent influenza consisted of either a fourfold rise in serum hemagglutination-inhibiting antibody or complement-fixing antibody from acute to convalescent specimens or the presence of significant levels of either antibody in one or more sera, as previously defined.[4]

Antibiotic-Sensitivity Tests.—Antibiotic disk-sensitivity tests on agar or horse-blood-agar plates were performed by standard methods, with use

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* Cases 1 to 11 in this paper correspond, in order, to Cases 16-19, 21, 23, 20, 22, and 24-26 in the previous paper.[4]

† The hospitals and the names of the referring pathologists and internists are as follows: Boston City (Drs. Fernando Biguria, Armand Lozano and Richard M. Zerkin), three cases; Newton-Wellesley (Dr. David Skinner), two, and Boston VA (Dr. Caesar G. Tedeschi), Faulkner (Dr. Phillip M. LeCompte), Lawrence General (Dr. Leslie S. Jolliffe), Milton (Dr. Phillip M. LeCompte), Mount Auburn (Drs. David Hurwitz and Rocco Latorocca), and Winchester (Drs. James E. Fitzgerald and Robert Lennon), one each.

TABLE 1.—*Certain Relevant Findings in Twenty Cases of Staphylococcal Pneumonia Complicating Asian Influenza A* **

Case	Sex	Age	Antecedent Disease	Onset Influenza to Onset Pneumonia, Days †	Findings When Severe Disease Was First Recognized ‡								
					Days After Onset of Influenza	Blood Pressure	Resp/ Min.	Cyanosis	Clinical &/or X-ray Findings			Bacteriology	
									Lobes Involved, No.	Bilateral Disease	Pleural Fluid	Sputum	Blood Culture
												Smear / Culture	
						A. Fatal Cases							
1	F	15	None	2	3	100/60	50	Yes	5	Yes	0	None produced	--
2	M	11	None	2	3	80/40 Shock	45	Yes	4	Yes	0	Staph. / Staph.	--
3	M	61	Bronchial asthma, Cor. H. D.	3	3	140/72	40	Yes	4	Yes	0	-- / Staph.	Neg.
4	F	19	None	3	5	70/36 Shock	28	Yes	2	Yes	0	None produced	Neg.
5	M	26	None	3	5	170/78	48	Yes	3	Yes	Bilateral	Staph. / Staph.	Staph.
6	M	29	None	4	8	130/75	44	Yes	4	Yes	Right	Staph. / Staph.	Neg.×2
7	F	41	Bronchial asthma	5	5	150/90	40	No	2	Yes	0	-- / --	--
8	M	59	Rheum. H. D.; pneumonectomy for Ca of lung	7	8	160/80	--	No	1	No	Right #	None produced	Neg.
9	M	57	Chronic bronchitis	9	11	110/80	35	Yes	2	Yes	0	Staph. / Staph.	Neg.
10	M	57	Bronchial asthma; Cor. H. D.	12	11	Shock	35	Yes	2	Yes	Bilateral	-- / --	--
11	M	62	Hyp. H. D.; old myocardial infarct	12	13	210/90	30	Yes	3	Yes	Right	None produced	--
						B. Nonfatal Cases							
12	F	19	Bronchial asthma	3	4	106/70	30	Yes	3	Yes	0	Staph. / Staph.	--
13	M	35	Obesity	4	9	170/110	28	No	2	No	0	Mixed flora / Staph.	Staph.×2
14	F	19	None	4	6	118/60	36	Yes	4	Yes	Right	Staph. / Staph.	Neg.×2
15	F	27	None	6	8	104/50	44	Yes	1	No	0	Staph. / Staph.	Neg.
16	F	71	Cor. H. D.	6	8	140/64	21	No	2	No	Right	Staph. / Staph.	Neg.×2
17	M	57	None	7	8	120/70	28	No	2	No	0	Gram pos. diplos. / Staph.	Neg.×2
18	F	23	None	7	8	100/50	28	No	1	No	0	Staph. / Staph.	Neg.
19	M	36	Epilepsy; alcoholism	7	8	130/82	20	No	2	No	0	Staph. / Staph.	--
20	M	27	Recent pneumococcal pneumonia	18	20	80/0 Shock	42	Yes	5	Yes	0	None produced	Staph.×3

TABLE 1.—*Certain Relevant Findings in Twenty Cases of Staphylococcal Pneumonia Complicating Asian Influenza A* *—Continued

Case	Sex	Age	Findings when Severe Disease was First Recognized ‡				Onset of Pneumonia to Start of Appropriate Antibiotic Therapy, Days §	Antibiotic Therapy ‖		Asian Influenza A Serology ¶		
			Bacteriology	White Blood Cells								
			Other Cultures	Count/ Mm.³	% Neutrophils	Clinical Working Diagnosis		During Pneumonia	Before Pneumonia	Days After Onset Influenza	CF	HI
						A. Fatal Cases						
1	F	15	Ts, staph.	--	--	Viral pneumonia; ?bronchopneumonia	?	T, P, S, **C**	--	3	128	20
2	M	11	--	6,800	20	Staphylococcal pneumonia	1	P, **E, C**	--	3	<8	<5
3	M	61	--	7,700	78	Influenzal pneumonia	?	T, P, S	--	4	16	5
4	F	19	Ts, normal flora § Staph.	4,800	59	Influenzal pneumonia, myocarditis	?	P	--	6	32	<5
5	M	26	--	5,500	4	Staphylococcal pneumonia	2	P, **E, C**	--	7	64	5
6	M	29	Pf, staph.	7,400	63	Staphylococcal pneumonia	4	**E, C, B, N**	--	8	8	10
7	F	41	--	16,000	86	Status asthmaticus	?	T	T, 4d	6	16	<5
8	M	59	Ts, normal flora § Staph.	15,000	72	Fever of unknown origin	?	T	T, 6d	--	--	--
9	M	57	--	20,000	64	Staphylococcal pneumonia	2	P, **C, E**	--	--	--	--
10	M	57	--	--	--	?Pulmonary embolus	?	T	T, 8d	--	--	--
11	M	62	--	9,300	82	Bronchopneumonia	?	P, S	--	17	128	40
						B. Nonfatal Cases						
12	F	19	--	3,500	76	Staphylococcal pneumonia	2	C, E 2d; then C, E, **N** 14d	P+S, 3d	8	128	20
13	M	35	--	19,000	83	Bronchopneumonia	6	P 1d; then P, **C, E** 1d; then P, **C, N** 15d	--	20	>512	40
14	F	19	--	14,000	85	Staphylococcal pneumonia	2	**C, E, B** 3d; then **C, E, B, N** 21d	P, 5d	5	64	<5
15	F	27	--	16,000	74	Staphylococcal pneumonia	5	P 2d; then **C, E** 19d	--	22	AC	20
16	F	71	--	12,000	64	Staphylococcal pneumonia	3	P 2d; then **C, E** 3d; then **C, E, N** 11d	--	7	256	10
17	M	57	--	11,000	74	Pneumococcal pneumonia	4	P 3d; then **C, E, B** 8d	**T**, 4d	22	512	40
18	F	23	Ts, normal flora	15,000	89	Staphylococcal pneumonia	1	**C, E** 12d	--	11	128	10
19	M	36	--	12,000	64	Staphylococcal pneumonia	4	**C, E** 10d	--	15	512	40
20	M	27	Ts, Str. hem.§ Staph.	6,000	82	Staphylococcal pneumonia	1	**C, N, B** 13d; then **N, V** 6d; then **V, B** 4d; then **V, E** 9d	T, 10d	9	64	20
										22	128	40
										12	32	<5
										9	16	5
										24	128	40
										11	<8	10
										32	64	20
										21	32	<5
										35	64	<5
										65	64	

of commercial disks ‡; zones of growth inhibition were interpreted as sensitive, moderately sensitive, or resistant, in accordance with standards recommended by the manufacturer. The antibiotics thus tested included penicillin, streptomycin, tetracycline, erythromycin, chloramphenicol, novobiocin, and—in about half the tests—bacitracin.

Sensitivities by the disk method were performed directly on specimens of sputum and of various body fluids shown to contain moderate to large numbers of staphylococci on Gram stain. A generous amount of sputum was taken up on a cotton swab and spread evenly on the surface of a blood-agar plate, and the disks were applied; with other fluids, either the contents of a well-moistened swab or a pipetted inoculum of 0.5 to 1.0 ml. was spread uniformly over the surface of a plate and the surface allowed to dry before the disks were applied. The direct sensitivity plates were examined at 4 to 6 hours in most instances and at 12 to 18 hours in all; during the early period of growth, zones of inhibition were best read by reflected light, with the aid of a $\times 3$ hand lens. All the strains were also isolated in pure culture and the majority tested for antibiotic sensitivity on agar plates into which were incorporated serial twofold dilutions of various antibiotics, with use of methods and standards previously described.[8]

Bacteriophage Typing.—Strains of pathogenic staphylococci were typed on the basis of lysis by staphylococcal bacteriophages Types 29, 52, 52A, 79, 3A, 3B, 3C, 55, 39, 523, 6, 7, 42E, 47, 53, 54, 70, 73, 75, 77, 42B, VA4, 42D, 44A, and 81 at the critical test dilution of bacteriophage; only if no reactions occurred were concentrated bacteriophages used.§

Results

Clinical Observations.—Characteristics of Fatal and Nonfatal Cases: The fatal and the nonfatal groups of patients were roughly similar in age and in types of antecedent disease (Table 1). The difference in distribution by sex was not significant.

The major clinical differences between the two groups (other than their hospital source) lay in the severity of disease, accuracy of etiologic diagnosis, and efficacy of the antibiotics administered.

‡ Brain Heart Infusion Agar and Bacto-Sensitivity Disks, Difco Laboratories, Detroit 1.

§ Performed by Elaine L. Updike, Chief, Staphylococcus and Streptococcus Unit, Communicable Diseases Center, U. S. Public Health Service, Chamblee, Ga.

* M indicates male; F, female; B, bacitracin; C, chloramphenicol; E, erythromycin; N, novobiocin; S, streptomycin; T, tetracycline; V, vancomycin; d, days therapy given; H. D., heart disease; Rheum., rheumatic; Cor., coronary; Hyp., hypertensive; ..., not done or unknown; Ts, throat swab; Pf, pleural fluid; Neg., no growth; Str. hem., hemolytic Streptococcus; Staph., Staphylococcus pyogenes var. aureus, coagulase-positive; diplos, diplococci.

† First appearance of dyspnea, pleuritic pain, or hemoptysis.

‡ When physician first consulted, or when attending physician first became aware of serious nature of the illness.

§ Treatment with antibiotic(s) to which infecting strain of staphylococcus was sensitive; ?, infecting strain of staphylococcus not sensitive to antibiotics administered.

‖ Bold face indicates antibiotics to which infecting strain of staphylococcus was sensitive.

¶ CF, complement fixation titer, HI, hemagglutination-inhibition titer vs. A/Jap 305/57 strain, expressed as reciprocal of initial serum dilution; AC, anticomplementary. Asian Influenza A virus was isolated from throat washings or postmortem tissues in Cases 2, 3 & 7 (see Ref. 4) and from none of the throat washings of 6 nonfatal cases (Nos. 12, 14, 15, 16, 18 & 19).

Side of operation.

Severity of Pneumonia: Although the courses and findings in the fatal cases were often very similar to those in the cases that recovered, the onset of pneumonia in the fatal cases tended to occur earlier in the course of the influenza (median: fourth day versus sixth day), and there was functional evidence of severer disease (Tables 1 and 2). When severe disease was first recognized in the patients who died, 8 were tachypneic, 9 were cyanotic and 11 had evidence of bilateral pulmonary involvement. In contrast, only three of the nonfatal cases were tachypneic, four were cyanotic, and three had findings of bilateral disease at the corresponding time.

TABLE 2.—*Comparison of Certain Clinical Features in Eleven Fatal and Nine Nonfatal Cases of Postinfluenzal Staphylococcal Pneumonia*

	Fatal Cases	Nonfatal Cases
Cases, no.	11	9
Age, yr. *	11-62	19-71
	40	35
Sex, male/female	8/3	4/5
Days after onset influenza that pneumonia occurred *	2-12	3-18
	5.6	6.9
Interval, between onset of pneumonia & start of specific chemotherapy, days * †	1-4	1-6
	2.3	3.1
Asian influenza A vaccine >14 days before onset of influenza	1	0
Findings when severe disease first recognized		
Severe hypotension	3/11	1/9
Respiratory rate/min.		
31-40	4/10	1/9
>40	4/10	2/9
Cyanosis	9/11	4/9
Chest findings, clinical or x-ray		
No. lobes involved, mean	2.9	2.4
Bilateral pulmonary involvement	10/10	3/9
Pleural fluid	5/11	2/9
WBC, thousands/mm.³ *	4.8-20	3.5-19
	10	12
% neutrophils *	4-86	64-89
	59	78
Correct etiologic diagnosis few hr. after severe disease first recognized	4/11	7/9
Specific chemotherapy †	4/11	9/9

* Range/mean.

† Antibiotics to which the infecting strain of Staphylococcus was sensitive.

Accuracy of Etiologic Diagnosis: In only 4 of the 11 fatal cases was a working diagnosis of staphylococcal pneumonia made within a few hours of the time when severe disease was first recognized; in them the diagnosis rested largely on demonstration of the presence of staphylococci in a Gram-stained sputum. In none of the remaining seven fatal cases was a stained specimen of sputum examined. In four cases no sputum was produced. In Cases 3 and 10 the patients' pink, frothy sputum was considered grossly consistent with pulmonary edema and smears were not made. In Case 7 the sputum was viscid and slightly purulent, resembling that which the patient usually raised during asthmatic attacks; it was, therefore, not examined.

In contrast, seven of the nine nonfatal cases were diagnosed promptly—six on evidence from the Gram-stained sputum. Cases 13 and 17 were mistakenly diagnosed, one as bronchopneumonia of uncertain etiology and the other as pneumococcal pneumonia, on the basis of microscopic examination of the sputum; later review of the smears showed predominant staphylococci in both preparations. In Case 20 the patient produced no sputum, but a working diagnosis of staphylococcal pneumonia was nevertheless made because of the circumstantial evidence of recent tetracycline therapy for proven pneumococcal pneumonia.

The various diagnostic entities with which staphylococcal pneumonia was confused in seven fatal cases and in two nonfatal cases are listed under the heading "Clinical Working Diagnosis" in Table 1. Erroneous diagnoses of either "viral" (influenzal or primary atypical) pneumonia or nonspecific bronchopneumonia were made particularly when the patient produced no sputum.

Specificity and Efficacy of Antibiotic Therapy: In only 10 of the 20 cases—3 fatal and 7 nonfatal—were potent antistaphylococcal chemotherapeutic agents promptly administered; in all 10, staphylococcal pneumonia had been promptly

diagnosed (Table 1). In Case 9, although the disease was accurately diagnosed, inadequate doses of otherwise potent antibiotics were given. In Cases 13 and 17, which were at first thought to be bronchopneumonia and pneumococcal pneumonia, effective chemotherapy was given after delays of one day and three days, respectively. In the remaining seven fatal cases, penicillin or tetracycline or multiple antibiotics with weak antistaphylococcal activity were used.

Although the antibiotic combination of erythromycin and chloramphenicol, with or without novobiocin, was most often associated with survival, the cases are too few and the treatment schedules too varied to state with certainty the superiority of any one effective regimen over another.

Clinical Response to Chemotherapy: Only in Case 17 of the nonfatal group could the clinical response to effective chemotherapy be described as "dramatic"; in the other eight cases, although staphylococci were markedly reduced or cleared from the sputum in a few days, an irregular fever in excess of 101 F rectally persisted for from four to 16 days (mean, 8.5 days), or until the fluids in all pulmonary cavitations or in empyemas had been either drained or resorbed.

"Prophylactic" Antibiotics and Staphylococcal Pneumonia: The possible role of broad-spectrum antibiotics or of combinations of antibiotics in predisposing the patient with otherwise uncomplicated influenza to staphylococcal pneumonia is strongly suggested in both groups of cases (Table 1). During and after their episode of influenza, and immediately preceding the appearance of symptoms of staphylococcal pneumonia, three patients who died and two who recovered had each received tetracycline for 4 to 10 days, and one of those who recovered had been treated with penicillin and streptomycin for 3 days. In only one of these six cases was the infecting strain of staphylococcus sensitive to the antibiotics previously administered.

Corticosteroid Therapy: Adrenocortical steroids were used in the treatment of six of the fatal cases in doses approximating 200 to 400 mg. of hydrocortisone per day; in contrast, similar corticosteroid therapy was employed in only one of the nonfatal cases. In view of the several other major differences between the fatal and the nonfatal groups, no conclusion can be drawn from this observation.

Laboratory Observations.—Properties of Staphylococci: Studies of the strains of staphylococci isolated from both groups of cases (Table 3) revealed a high incidence of antibiotic resistance and a rather restricted spectrum of bacteriophage types. The strains from all but 1 of the 20 patients were highly resistant to penicillin, and 14 were resistant to streptomycin; 10, to tetracycline, and 6, to erythromycin. In contrast, only three were highly resistant to chloramphenicol and none to novobiocin, bacitracin and, with few exceptions, the newer antistaphylococcal antibiotics.

Bacteriophage typing of strains of staphylococci from 15 patients demonstrated specific lysis by Phages 42B or 42B and 81 in 13 and by Phages 42D, 52A, and 79 in the two others. The 13 strains with related Phage types were derived from patients at seven different hospitals who were residents of nine different communities in and near metropolitan Boston. Epidemiological evidence suggested that eight of the patients who yielded the 13 related strains presumably acquired them in the community; three probably acquired their strains in the hospital, and two possibly did.

Rapid Choice of Effective Antibiotics: In three fatal and eight nonfatal cases rapid confirmation of the effectiveness of antibiotics prescribed by the attending physician was afforded by the results of disk sensitivity tests made directly on sputum or other infected body fluids. With the method described, the antibiotic sensitivities of staphylococci in a specimen in which they predominated could be read with considerable accuracy at 4 to 6 hours in a quarter of the tests, and at 12 to 18 hours

TABLE 3.—*Certain Properties of Staphylococci from Twenty Cases of Pneumonia Complicating Asian Influenza*

Case	Source	Hemolytic †	Coagulase 30 Min.	Coagulase 24 Hr.	Sensitivity to Antibiotics by Plate-Dilution (μg/Ml.) or Disk Method P	Sm	T	E	C	N	B	V	Om	Spm	Sy	Probable Source of Infection	Bacteriophage Pattern
					A. Fatal Cases												
1	L *	±	+	+	>100	100	100	0.4	3.1	0.1	25	6.3	1.6	50	100	Community	42B/52/81
2	Sp	+			>100	6.3	0.8	0.4	12.5	0.2	12.5	3.1	1.6	25	50	Community	42D/52A/79
	L	+	+	+	25	6.3	0.8	0.8	12.5	0.2	12.5	6.3	3.1	50	50	Community	42D/52A/79
3	Ts	0	0	+	>100	>100	100	0.8	3.1	0.2	25	6.3	1.6	25	100	Community	42B/52/81
4	Ts ‡	+	+	+	25	3.1	0.4	0.8	3.1	0.2	50	6.3	1.6	25	25	Community	42B/81
5	Sp	+			R	S	S	S	S	S						Community	
	B	+			>100	3.1	0.8	0.4	6.3	0.1	25	6.3	1.6	50	100	Community	
	L	+	+	+	>100	3.1	0.8	0.4	6.3	0.1	25	6.3	1.6	50	100	Community	42B/52/81
6	Sp	+	+	+	>100	>100	100	0.8	6.3	0.2	25	6.3	1.6	25	100	Hospital	42B/52/81
7	L	+	+	+	>100	>100	>100	>100	3.1	1.6	25	25	6.3	25	>100	? Hospital	42B/81
8	Sp	+	+	+	>100	>100	100	>100	3.1	0.2	25	6.3	3.1	50	>100	Hospital	42B
	L	+	+	+	>100	>100	100	>100	3.1	0.2	25	6.3	3.1	50	>100	Hospital	42B
9	L	+	+	+	>100	>100	100	0.8	3.1	0.2	25	6.3	1.6	25	100	Community	42B/52/81
10	L	±	0	0	>100	100	100	0.4	6.3	0.2	25	6.3	1.6	50	100	Hospital	42B/52/81
11	Staphylococci seen in Gram-Weigert stained sections of lung—not available for study																
					B. Nonfatal Cases												
12	Sp	+	+	+	>100	>100	>100	>100	>100	0.1	50	6.3	3.1	50	>100	? Hospital	6/42B/42E/47/81
13	Sp	+			S	R	R	R	S	S						Community	
	B	0			R	S	S	S	S	S						Community	
14	Sp	+	+	+	>100	>100	1.6	>100	6.3	0.2	50	6.3	6.3	50	>100	Community	42B/52/81
15	Sp	+	+	+	>100	>100	1.6	>100	50	0.2	50	6.3	3.1	50	>100	Community	42B/81
16	Sp	+			R	R	S	S	S	S						Community	
17	Sp	+			R	S	S	S	S	S						Community	
18	Sp	0	0	+	50	3.1	1.6	0.4	6.3	0.4	12.5	3.1	1.6	25	12.5	Community	42D/52A/79
19	Sp	+	+	+	25	100	0.8	0.8	3.1	0.2	50	6.3	3.1	25	25	Community	42B/81
20	B	+			R	R	R	R	S	S						Hospital	

* L indicates lung post mortem; Sp, sputum collected at time of admission to hospital; Ts, tracheal secretion post mortem; B, blood culture ante mortem; 0, negative; +, positive; ±, weakly positive; S, sensitive; R, resistant; P, penicillin; Sm, streptomycin; T, tetracycline; E, erythromycin; C, chloramphenicol; N, novobiocin; B, bacitracin; V, vancomycin; Om, oleandomycin; Spm, spiramycin; Sy, synnematin B.

† Surface growth on agar containing 10% horse blood; all strains produced golden yellow pigment.

‡ Strain with identical properties, including sensitivity to antibiotics and bacteriophage pattern, was isolated from lung post mortem.

TABLE 4.—*Comparison of Disk Sensitivity Tests on Pure Cultures of Pathogenic Staphylococci and Directly on Original Sputa and Body Fluids*

	Pure Cultures of Staphylococci *	Direct Culture †	
		Sputa *	Body Fluids ‡
Specimens tested, no.	25	42	17
Tests readable at 12-18 hr.		41	17
Tests readable at 4-6 hr.		9/35	7/17
False-sensitive disk readings at 4-6 hr.		0/57	2/47
Specimens subsequent serial plate dilution sensitivity test on pure culture, no.	25	11	5 §
False-sensitive disk readings on original test	5/166	5/70	2/33

* From cases of fatal and nonfatal staphylococcal pneumonia, September, 1957, through May, 1958, Boston City Hospital.

† Moderate to large numbers of staphylococci on Gram stain.

‡ Abscess exudates, 10; pleural fluids, 4; joint fluids, 2, blood cultures, 1.

§ Subsequent disk sensitivity test on pure culture.

in virtually all (Table 4). Interpretation of zones of inhibition was complicated in 10 of 42 sputum specimens and in 1 of 17 body fluids by the growth of colonies of coliform or other Gram-negative organisms or of Candida species; in all instances but one, these colonies could be differentiated from staphylococci by inspection or by a Gram stain and the interpretation thus clarified. Despite the crudeness of the method, the accuracy of the technique compared favorably with that of disk sensitivity tests done on pure cultures (Table 4).

Comment

During the past decade, concomitant with the intensive and widespread use of antibiotics, the Staphylococcus has assumed ever-growing importance as a respiratory pathogen. The pandemic of Asian influenza A of 1957-1958 was the first in which, in nearly all parts of the world, the Staphylococcus played the dominant role in the pneumonias complicating influenza.

Although fulminant postinfluenzal staphylococcal pneumonia was recognized as early as the 1889-1890 influenza pandemic[6,7] and noted in localized outbreaks during the pandemic of 1918-1919,[8-10] it was considered of relatively minor importance compared to postinfluenzal pneumococcal, streptococcal, and Hemophilus influenzae pneumonia until the early 1940's.[11-13] Studies from this laboratory at that time,[12] when sulfonamides were the only active chemotherapeutic agents available, emphasized the wide spectrum of clinical forms and degrees of severity of postinfluenzal staphylococcal pneumonia and suggested the probability of future widespread postinfluenzal staphylococcal pneumonia in communities in which pathogenic staphylococci are known to be prevalent prior to the epidemic. The cases observed here in the 1940-1941 outbreak were divided into six groups, of which the three most important were (1) acute, rapidly fatal, usually bilateral pneumonia, 7 cases; (2) severe, but less rapidly progressive, pneumonia marked by persistent dyspnea and cyanosis and ending in death after two to eight weeks, 6 cases, and (3) moderately severe pneumonia, involving one or two lobes, responding to chemotherapy with fall in temperature and recovery in one to four days, 18 cases. A comparison of the data in these cases with those in the present series suggests that in the intervening seventeen years considerable progress has been made in saving patients like those of Group 2, who otherwise would probably have died (Cases 12, 14, and 20), but that despite the availability and potency of modern antistaphylococcal antibiotics very limited progress has been made in saving the lives of patients like those of Group 1.

Accounting in part for this continuing mortality is probably the nature of the pathologic process itself. Fatal Cases 2, 5, and 6 illustrate the inexorably progressive form of the disease, overwhelming the patient despite accurate diagnosis, prompt administration of potent antibiotics, and clearing of staphylococci from the sputum. These cases epitomize the role of asphyxia in severe staphylococcal pneumonia—asphyxia due both to destruction of pulmonary parenchyma and to plugging of bronchioles with edema, hemorrhage, and

exudate [13,14]—and underscore the pressing clinical need for an "artificial lung," capable of extrapulmonary gaseous exchange, to tide patients over the phase of acute respiratory insufficiency.

A second, perhaps more important, explanation for the continuing mortality of Group 1-like cases is the paradox revealed by comparison of the fatal and the nonfatal cases: the patients with the severest disease were generally the least accurately diagnosed and, therefore, received the least effective antibiotic therapy. Diagnosis of this group of patients was exceptionally difficult; not only did their sputum tend to be absent, scanty, or atypical, but their roentgenographic and laboratory findings were virtually indistinguishable from those found in cases of severe pure influenzal pneumonia.[4]

That a specific etiologic diagnosis of staphylococcal pneumonia was of fundamental importance, inasmuch as it directed the attention of the attending physician to specific antistaphylococcal antibiotic choices, is revealed by the properties of the staphylococci themselves. The most striking characteristic of the organisms associated with both the fatal and the nonfatal cases was the exceptionally high incidence of strains resistant to multiple antibiotics—strains hitherto associated with hospital-acquired rather than community-acquired infections. The data demonstrate that at least in the area of Boston and environs, penicillin, streptomycin, and tetracycline can no longer be relied upon as effective agents in the treatment of postinfluenzal staphylococcal pneumonia. That 6 of the 20 strains tested were resistant to erythromycin suggests that this drug, in general use less than five years, may soon join the list.

Consistent with the high degree of antibiotic resistance of the strains studied was the restricted distribution of their bacteriophage types. Data from community surveys in several cities in the United States [15-17] and from surveys of strains involved in hospital infections in major cities throughout the world [18,19] suggest that strains lysed by Phage Types 42B or 81 || or both and those of Phage Pattern 42D/52A/79 are relatively unusual in healthy members of the community but very common in hospitals, where they constitute a large proportion of the antibiotic-resistant strains. The emergence of these strains in the community raises the question of the degree to which hospital strains are seeding the community, as demonstrated by Colbeck [21] and by Jackson, Dowling, and Lepper.[16,22]

Once having made the diagnosis of staphylococcal pneumonia and initiated therapy with one or more properly chosen antibiotics, the attending physician often remained in doubt for hours or for days concerning the efficacy of his therapeutic choices, since the patient's fever, dyspnea, chest pain, and, when present, cyanosis and leukocytosis commonly persisted for several days and since follow-up stained smears of sputum frequently continued to show moderate numbers of staphylococci. Attending physicians were therefore often strongly tempted to change antibiotics, to administer one or more additional antibiotics, or to resort to desperate therapeutic measures of unproved benefit.

In these circumstances the data derived from disk sensitivity tests performed directly on sputum or infected body fluids proved of considerable value. Since relatively accurate readings of the antibiotic sensitivities of staphylococci in such tests could be made in 4 to 6 hours in a quarter of the specimens, and in 12 to 18 hours in almost all, the attending physician was afforded a reasonably reliable check on his antibiotic choices at the time when he needed such information, rather than hours to days later. The inaccuracies of disk sensitivity

|| Because of data indicating that Phage Types 42B and 52 have undergone laboratory variation and now lyse strains of Phage Types 80 and 81,[20] strains with the basic Phage Pattern 42B/52/81 or 42B/52/80/81 are now considered essentially identical and are designated as Type "80/81" by the International Typing Reference Center.[19]

tests, particularly with respect to false-sensitive readings, have troubled many workers[23,24] and have recently been reinvestigated.[25] Such inaccuracies were of relatively minor importance in the present experience, however, at least with staphylococci (Table 4).

The importance of speed in both the diagnosis of postinfluenzal staphylococcal pneumonia and the institution of specific chemotherapy was noted in the previous paper of this series; the mean and median intervals in the fatal cases between the time when severe disease was first recognized (when a physician was first consulted or when the physician in attendance first became aware of the serious nature of the illness) and the time that death occurred were, respectively, 1.4 days and 1 day.[4] It was also demonstrated that except when staphylococci were seen in the stained smears of the sputum or when pulmonary cavitation was evident in the roentgenograms, severe cases of pure influenzal pneumonia and of postinfluenzal staphylococcal pneumonia were virtually indistinguishable, clinically.

In the light of these data, it is apparent that during epidemics of influenza in localities in which staphylococci are known to be prevalent, all patients with the signs of severe, potentially fatal influenza should—until proven otherwise—be diagnosed and treated promptly as cases of staphylococcal pneumonia caused by relatively antibiotic-resistant staphylococci.

Summary

The clinical and laboratory findings in 11 fatal and 9 nonfatal cases of staphylococcal pneumonia complicating Asian influenza A in the Boston area are compared. The fatal cases were generally marked by severer and more rapidly progressing illness, less accurate diagnosis, and relatively ineffective antibiotic therapy.

Although most of the 20 cases arose in the community rather than in hospitals, the strains of staphylococci responsible were commonly resistant to multiple antibiotics and were of bacteriophage types most often associated with hospital-acquired infections.

Disk sensitivity tests performed directly on sputum or body fluids containing staphylococci afforded a rapid, relatively accurate guide for the selection of effective antibiotics.

It is suggested that during epidemic influenza in areas where major staphylococcal infections are common all patients with the signs of potentially fatal influenza be diagnosed and treated promptly as cases of staphylococcal pneumonia caused by the prevalent types of antibiotic-resistant staphylococci until the diagnosis can be disproved.

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Augmentation

A Third Stage of Digitalis Therapy

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William Withering, in 1785, stated, in referring to digitalis: "Let the medicine therefore be given in the dose and at the intervals mentioned above:—let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any of these effects."[1] Since that time, however, it has become common medical practice to digitalize a patient initially and then to assume that a full effect will persist with an average maintenance dose. The purpose of this report is to call attention to a third stage of digitalization, following those of initial digitalization and maintenance: that of periodic augmentation.

Subject and Methods

Thirty-three patients were studied. Eighteen of them had been digitalized by other physicians in the conventional manner and maintained on an average maintenance dose without interruption for periods varying from 1 month to 15 years. Eleven had received powdered leaf, four digitoxin, two gitalin, and one digoxin. The daily maintenance dosage had been that usually employed for these several preparations. These patients had been considered to be adequately digitalized and were referred to us as problems in the management of "refractory" congestive heart failure. They represented an average sampling of chronic congestive heart failure. Thirteen had normal sinus rhythm, and three had auricular fibrillation. In order to learn whether these subjects were in fact adequately digitalized, we administered gitalin three to four times daily after meals, in total daily doses of 1.5 to 4 mg. More recently, all patients have received supplemental doses of potassium chloride, 1 gm. with each dose of gitalin. Although most of the subjects were hospitalized, they were taught to take the drug on their own responsibility rather than from a nurse. They were carefully instructed to watch for a sudden decrease in appetite, nausea, vomiting, or diarrhea and told to omit the drug after any one of these symptoms until seen by a physician. Each subject was seen one to four times daily by a doctor in order to detect a new arrhythmia or an increase in a preexisting arrhythmia. In five patients, 100 gm. of glucose was given orally and an ECG was taken 30 to 45 minutes later. The purpose was to learn whether they were close enough to mild cardiotoxicity for precipitation of arrhythmias by temporary electrolyte imbalance, as reported by Page.[2] When a toxic symptom or sign was noted, the digitalis was omitted until the symptoms completely subsided and was reinstated at an appropriate maintenance dose. Electrocardiograms were not taken routinely at the time of toxicity, except in the presence of an arrhythmia. The onset of auricular fibrillation was considered a toxic manifestation, despite the possibility that its occurrence might represent a pharmacologic action.

The dose of gitalin necessary to produce minimal toxic effects was calculated by subtracting from the total dose administered under observation an amount thought to represent the probable daily dissipation (excretion and destruction) of the drug. Since the average maintenance dose of gitalin is between 0.5 and 1.0 mg. per day, two figures were obtained, one by subtracting 0.5 mg. per day and one by subtracting 1.0 mg. per day, with the amount of supplementary gitalin retained assumed to lie between the two values. Objective measurements of improved cardiac function were weight loss, decrease of venous pressure, shortened circulation time, increased vital capacity, disappearance of crepitant rales from the lungs, decrease in edema, disappearance of diastolic gallop, or reduction in neck vein distention or hepatic enlargement. In five instances, recordings of precordial movements as described by Eddleman et al.[3] were made before and after the augmentation of digitalis dosage. These tracings were studied for the presence of evidence of improved cardiac contraction. Finally, it was noted whether there

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TABLE 1.—*Amount of Gitalin Tolerated by Patients Previously Thought to Have Been Completely Digitalized* *

Subject No.	Rhythm	Previous Digitalis Therapy, Duration	Digitalis Previously Used, Type	Deficit from Digitalis Intoxication, † Mg. Gitalin		Subjective Improvement	Objective Improvement		Other Treatment
				A	B		Occurrence	Manifestations	
1	NSR	5 mo.	Leaf	1.0	3.5	Yes	No	--	--
2	NSR	15 yr.	Digitoxin	1.5	3.0	Yes	Yes	10 lb. wt. loss; disappearance of rales & PVC	Mercaptomerin; acetazolamide
3	AF	2 wk.	Digitoxin	5.0	8.0	Yes	No	--	--
4	NSR	6 mo.	Digitoxin	1.0	3.5	?	No	--	--
5	NSR	4 mo.	Leaf	3.0	6.0	Yes	Yes	7 lb. wt. loss; V. C. inc. from 1.9-2.1 L.; rales & gallop disappeared	Meralluride
6	NSR	1 yr.	Leaf	5.0	10.0	Yes	Yes	21 lb. wt. loss	Mercaptomerin; acetazolamide
7	NSR	4 mo.	Gitalin	2.5	5.0	Yes	No	--	--
8	NSR	5 yr.	Leaf	2.5	5.5	Yes	Yes	5 lb. wt. loss; dec. in orthopnea	No
9	NSR	1 mo.	Leaf	5.5	8.0	Yes	Yes	4 lb. wt. loss: CT dec. from 40-30 sec.; VC inc. from 3.0-3.2 L.	No
10	NSR	4 yr. 3 mo.	Leaf gitalin	3.0	4.5	Yes	No	--	--
11	NSR	1 mo.	Digoxin	2.0	4.5	?	?	--	--
12	NSR	6 mo.	Leaf	0	2.5	?	?	Disappearance of rales & PVC	No
13	NSR	8 mo.	Leaf	5.0	8.5	Yes	Yes	3 lb. wt. loss; VP dec. from 150-110 mm. saline; ankle edema dec.; KCG improved	No
14	AF	2 yr.	Leaf	20.0	32.5	Yes	Yes	VP dec. from 120-80 mm. saline; CT dec. from 24-20 sec.; VC inc. from 3.0 to 3.2 L.	No
15	AF	3 yr.	Digitoxin	10.5	15.0	Yes	Yes	18 lb. wt. loss; VP dec. from 165-75; VC inc. from 2.8-3.2 L.; rales disappeared	No
16	NSR	1 mo.	Leaf	1.0	2.5	Yes	Yes	6.5 lb. wt. loss; liver dec. in size; neck vein distention dec.; KCG improved	No
17	NSR	3 yr.	Leaf	2.5	6.5	Yes	Yes	VP dec. from 230-195; CT dec. from 35-25 sec.; VC inc. from 3.4-3.6 L.	No
18	AF	15 yr. 7 mo.	Leaf gitalin	3.5	5.5	Yes	Yes	12 lb. wt. loss; VC inc. from 2.0-2.3 L.; CT dec. from 26-22 sec.	Bed rest

* These 18 patients were all sent to University Hospital supposedly completely digitalized and in digitalis-resistant heart failure. NSR indicates normal sinus rhythm; AF, auricular fibrillation; PVC, premature ventricular beats; VC, vital capacity; CT, circulation time (arm to tongue); VP, venous pressure.

† Expressed as milligrams of gitalin administered in excess of (*a*) an assumed sum of excretion and destruction of 1.0 mg. per day; (*b*) an assumed sum of excretion and destruction of 0.5 mg. per day.

were other measures employed which might have contributed to the improvement. The changes in the salt content of the diet or in the amount of activity from that prior to admission may have been factors in some cases. However, most of the patients had been under similar regimens and many of them had been in other hospitals immediately prior to admission to the University Hospital.

Four of the patients were not admitted but were seen daily as outpatients, and no change in their management was made other than the augmentation of digitalis.

Possible toxic manifestations other than anorexia, nausea, vomiting, diarrhea, and cardiac arrhythmias were occasionally observed. They consisted of lassitude, blurring of vision, and neurological symptoms. However, these were not included in our tabulation because they were not always sought after and when present were often of dubious significance as regards toxicity.

Results

The amount of gitalin assumed to have been retained is indicated in Table 1. Of the 18 patients considered by the referring physician to have been fully digitalized, either 6 or 11, depending on which estimate of daily dissipation is accepted, were able to retain at least 5 mg., which is in the range of the initial digitalization dose of gitalin. Twelve or eighteen were able to retain 2.5 mg. or more.

Fifteen of the eighteen patients were noted to have subjective improvement, usually manifested by increased exercise tolerance. There was no undoubted subjective improvement in the remaining three. Objective evidence of improved cardiac function was found in 11 of 18 patients, and in 7 of these no other measures were used which could have been assumed to be contributory to this result.

TABLE 2.—*Toxic Manifestations* *

	No.	%
Anorexia alone	6	
Anorexia plus other gastrointestinal symptoms	19	75.8
Gastrointestinal symptoms plus cardiotoxicity	5	
Cardiotoxicity alone	3	24.2
Total	33	

* Described in greater detail in text.

Toxic effects in these patients and in all others in whom gitalin was pushed in a similar manner are seen in Table 2. Of the 33 patients, 25, or approximately 75%, showed gastrointestinal symptoms without cardiotoxicity, and in 5 of these patients arrhythmias could not be precipitated by oral glucose and withholding of potassium. Six of these patients had clear-cut anorexia as the sole evidence of digitalis intoxication. Eight, or approximately 25%, had evidence of cardiotoxicity, and in only three of these was this the only manifestation of intoxication. The manifestations of cardiotoxicity were the appearance of premature ventricular contractions in three, an increase in preexisting premature ventricular contractions in two, one of which developed a bigeminal rhythm, and the onset of auricular fibrillation in three. However, only two of these eight patients were receiving supplemental potassium chloride as was given to those more recently studied, and in both of these the manifestation was auricular fibrillation. In one of these patients, the arrhythmia did not disappear on stopping digitalis and required conversion by quinidine.

The manifestations of toxicity lasted several hours to four days, usually completely disappearing within one day. In only 2 of the 33 patients was vomiting associated with the anorexia and nausea. In none of the other patients was mild digitalis intoxication associated with particularly unpleasant symptoms.

Report of Cases

CASE 1.—A 41-year-old white woman with a 15-year history of congestive failure secondary to rheumatic heart disease had had a mitral valvulotomy seven months before. She had received digitalis intermittently for six years and consistently for the last seven months. She had auricular fibrillation at a rate of 60 per minute, which increased to 82 per minute after exercise. Blood pressure was 110/60; neck veins were distended in the upright position; a large pulsatile liver was felt 3 fingerbreadths below the right costal margin; there was moderate ankle edema. There was an anterior sternal lift which was suggestive of right ventricular hypertrophy; a loud

P_2 and an opening snap of the mitral valve, murmurs indicating mitral stenosis, and possible tricuspid stenosis and insufficiency were heard.

Digitalis was pushed, and on the fourth day, after 7.0 mg. (or 3.5 to 5.5 mg. more than an estimated maintenance dose) she developed anorexia and nausea. The nausea lasted only a few minutes, and the anorexia lasted for one day. Evidence of objective improvement was a 12 lb. weight loss, a decrease in circulation time from 26 to 22 seconds, and a rise of vital capacity from 2.0 to 2.3 liters. No medication other than digitalis was given.

Comment.—This patient had been receiving the usual maintenance dose of digitalis and had been thought to be completely digitalized; however, the amount of gitalin taken before toxic symptoms developed and the rapid improvement indicated inadequate digitalization despite the slow rate.

CASE 2.—A patient had a seven-year history of coronary disease with at least one old myocardial infarction and congestive failure for three years. In association with the onset of auricular fibrillation, dyspnea had become progressively worse for four months, and one month prior to admission his maintenance dose of digitoxin was increased to 0.2 mg. per day. He had been receiving chlorothiazide, meralluride (Mercuhydrin) 2 ml. twice a week, a low-salt diet, and glyceryl trinitrate (nitroglycerin) as needed. For two of the four weeks before admission he had been in another hospital. Meralluride injections were often followed by abdominal cramps, nausea, and black spots before his eyes. Physical examination revealed an obese, dyspneic white man. His apical rate was 120 per minute; radial rate, 104. After exercise the apical rate rose to 144 per minute. Blood pressure was 140/90; respirations, 32; neck veins were distended in the upright position; liver was down 4 fingerbreadths and tender. There was no ankle edema; crepitant rales were present bilaterally. Examination of the heart revealed two separate precordial bulges on palpation; no significant murmurs and no gallop rhythm were present. ECG's showed left bundle-branch block and rapid auricular fibrillation.

Gitalin was pushed, and he received 18.5 mg. in nine days (10.5 mg. above maintenance of 1.0 mg. per day, or 6.5 mg. above a maintenance of 1.5 mg. per day) before minor toxic symptoms occurred. These were anorexia, nausea, and weakness. The anorexia lasted one day. He complained of black spots before his eyes from time to time, which would often appear after meals and were diminished in frequency when he was put on potassium chloride. His serum potassium was normal. He developed no visual symptoms the day toxicity developed, despite 100 gm. of glucose and omission of potassium in an attempt to determine if this symptom was related to temporary electrolyte imbalance. Evidences of objective improvement were an 18 lb. weight loss, disappearance of rales in the lungs, diminished distention of neck veins, decrease in the size of the liver, and disappearance of orthopnea and paroxysmal nocturnal dyspnea. His pulse rate decreased from 85 per minute to 68 per minute. The pulse rate after a standard exercise declined from 144 to 120, and, finally, to 90. The venous pressure diminished from 165 mm. of saline to 75 mm. Vital capacity increased from 2.8 liters to 3.2 liters. There was no other change in his regimen from that maintained prior to admission. He was put on a maintenance dose of 1.5 mg. of gitalin for five days, and no toxicity developed prior to discharge.

Comment.—This illustrates the enormous requirement of digitalis in some patients, which cannot be appreciated unless the drug is pushed. The presence of the nausea and black spots, present prior to admission, were shown to be unrelated to digitalis intoxication. The amount of digitalis required to produce optimal slowing of his pulse was about 85% of that of the toxic dose, illustrating the narrow margin between the therapeutic effectiveness and toxicity seen in some patients.

CASE 3.—A 40-year-old white man had a history of rheumatic fever at the age of 21. He had had congestive failure for three years. At that time he was digitalized and maintained on 0.1 gm. of digitalis leaf per day. Physical examination revealed a pulse of 60 per minute, which increased to 80 per minute after exercise. Blood pressure was 140/90 mm. Hg. Examination of the heart revealed a P. M. I. 1 cm. lateral to the midclavicular line and tapping in quality. M_1 was greater than M_2 and split. P_2 was greater than A_2 and split. There was a Grade 2 systolic murmur at the apex, a Grade 2-3 prolonged apical diastolic rumble, and a Grade 2 blowing diastolic murmur in the second and third left interspaces. The remainder of the examination was negative.

The patient was pushed on digitalis as an outpatient. For two weeks he was given 1.5 mg. per day. At the end of that time his pulse had decreased to 48 per minute at rest and between 65 and 70 per minute after exercise and remained at that rate for the next two weeks of the study. He was then given 2.0 mg. per day for one week, without development of toxicity, and after 2.5 mg. per day for four days he developed anorexia and nausea with no ECG changes. His total dose was 20 mg. above a maintenance of 1.0 mg. per

day, or 7.5 mg., assuming a maintenance dose of 1.5 mg. per day. The anorexia lasted less than one day. Objective evidences of improvement were a venous pressure decrease from 120 to 80 mm. of saline, vital capacity increased from 3.0 to 3.2 liters, and circulation time decreased from 24 seconds to 20 seconds. There was no other change made in his regimen.

Later, he was admitted to the hospital and cardiac catheterization was done. On the basis of this evaluation, surgery was recommended and he was sent out for six weeks on anticoagulants prior to valvulotomy. However, he was placed on only 0.1 gm. of digitalis leaf per day as a maintenance dose. When he returned to the hospital, he had a pulse rate of 70 to 80 per minute and was thought by the house staff to be adequately digitalized. However, on the morning when operation was planned, he was given premedication of atropine, 1/150 grain (0.43 mg.), and his pulse rate rose to 140 per minute. He was then transferred to the Medical Service, and digitalis was augmented. After this, valvulotomy was performed without complication.

Comment.—This patient's bradycardia occurred well before digitalis intoxication. The failure to appreciate the requirements of some patients for digitalis, and subsequent underestimation of the degree of digitalization, may lead to untoward results.

CASE 4.—A man with a 12-year history of coronary disease, angina, and two myocardial infarctions, had developed congestive failure following "pneumonitis" two months before referral. At that time, he was digitalized and maintained on 0.5 mg. of gitalin per day. He had also been taking quinidine, chlorothiazide, meralluride, and anticoagulants. Two weeks prior to admission his gitalin was stopped because of loss of appetite and bigeminy; it was restarted 10 days later on a dose of 0.5 mg. per day. His appetite remained only fair, and his cardiac irregularity persisted. On admission his pulse rate was 84 per minute, with bigeminy. Blood pressure was 105/70; respirations, 20. The patent appeared thin and chronically ill. Pulsatile distended neck veins were seen at 45 degrees. There were bilateral crepitant rales in the lungs. The liver was down 2 fingerbreadths and nontender. Examination of the heart revealed a prominent P. M. I. at the midclavicular line. P_2 was louder than A_2. There was a fairly well-localized Grade 2-3 apical systolic murmur not increased on inspiration and an inconsistent apical diastolic gallop. A second systolic murmur, loudest at the left lower parasternal area, transmitted to the right and increased by inspiration, was also noted. He was thought to have mild digitalis intoxication on admission, and digitalis was omitted for three days. After that time, gitalin was pushed, and he received 7.5 mg. over the next five days, or 2.5 to 5 mg. above a maintenance dose, before anorexia and nausea appeared. Both were gone by the next morning. He lost 12 lb., and his murmur of tricuspid insufficiency disappeared. He was also receiving acetazolamide and mercaptomerin (Thiomerin).

Comment.—Anorexia and nausea in patients with congestive heart failure on digitalis may be due to causes other than excessive digitalis. This may result in the physician's failing to obtain maximal benefit from digitalis. Among these other causes are hepatic congestion, as in this case, in which situation the liver will usually be tender, a finding seldom seen in patients with digitalis intoxication. Other causes for nausea and vomiting in these patients are concomitant unsuspected uremia or drugs such as ammonium chloride, aminophylline, or morphine.

CASE 5.—A 38-year-old white woman with a 30-year history of rheumatic fever had congestive failure for 18 years and had been on digitalis for four years. She entered the hospital with a 10-day history of "flu," with cough, and a three-day history of increased dyspnea, weakness, edema, and nausea. Blood pressure was 96/70 mm. Hg; she had auricular fibrillation at a rate of 96 to 110, and there were wheezes and inspiratory and expiratory rales bilaterally in both lung fields. The heart was enlarged, with a heaving precordial impulse. Murmurs of mitral stenosis, aortic insufficiency and possibly mitral insufficiency, and aortic stenosis were heard. The liver was felt down 2 fingerbreadths and was tender. There was minimal ankle edema.

While in the hospital she had frequent episodes of chest pain followed by nausea and vomiting and on one occasion associated with hemoptysis. A diagnosis of pulmonary emboli was made, and she was started on anticoagulants, and given concentrated opium (Pantopon) or dihydromorphinone (Dilaudid) for pain. Because of nausea and vomiting, her physician stopped digitalis, and over a two-week period her congestive failure became progressively severer. At that time, she was seen by a consultant who advised redigitalization, and this resulted in striking clinical improvement. The frequency of the chest pains gradually subsided; signs and symptoms of congestive failure disappeared, and she was discharged from the hospital free of symptoms. Three months later, she was admitted to the hospital with sudden onset of right upper quadrant pain, nausea and vomiting, and a right upper quadrant mass. At operation she was

P_2 and an opening snap of the mitral valve, murmurs indicating mitral stenosis, and possible tricuspid stenosis and insufficiency were heard.

Digitalis was pushed, and on the fourth day, after 7.0 mg. (or 3.5 to 5.5 mg. more than an estimated maintenance dose) she developed anorexia and nausea. The nausea lasted only a few minutes, and the anorexia lasted for one day. Evidence of objective improvement was a 12 lb. weight loss, a decrease in circulation time from 26 to 22 seconds, and a rise of vital capacity from 2.0 to 2.3 liters. No medication other than digitalis was given.

Comment.—This patient had been receiving the usual maintenance dose of digitalis and had been thought to be completely digitalized; however, the amount of gitalin taken before toxic symptoms developed and the rapid improvement indicated inadequate digitalization despite the slow rate.

Case 2.—A patient had a seven-year history of coronary disease with at least one old myocardial infarction and congestive failure for three years. In association with the onset of auricular fibrillation, dyspnea had become progressively worse for four months, and one month prior to admission his maintenance dose of digitoxin was increased to 0.2 mg. per day. He had been receiving chlorothiazide, meralluride (Mercuhydrin) 2 ml. twice a week, a low-salt diet, and glyceryl trinitrate (nitroglycerin) as needed. For two of the four weeks before admission he had been in another hospital. Meralluride injections were often followed by abdominal cramps, nausea, and black spots before his eyes. Physical examination revealed an obese, dyspneic white man. His apical rate was 120 per minute; radial rate, 104. After exercise the apical rate rose to 144 per minute. Blood pressure was 140/90; respirations, 32; neck veins were distended in the upright position; liver was down 4 fingerbreadths and tender. There was no ankle edema; crepitant rales were present bilaterally. Examination of the heart revealed two separate precordial bulges on palpation; no significant murmurs and no gallop rhythm were present. ECG's showed left bundle-branch block and rapid auricular fibrillation.

Gitalin was pushed, and he received 18.5 mg. in nine days (10.5 mg. above maintenance of 1.0 mg. per day, or 6.5 mg. above a maintenance of 1.5 mg. per day) before minor toxic symptoms occurred. These were anorexia, nausea, and weakness. The anorexia lasted one day. He complained of black spots before his eyes from time to time, which would often appear after meals and were diminished in frequency when he was put on potassium chloride. His serum potassium was normal. He developed no visual symptoms the day toxicity developed, despite 100 gm. of glucose and omission of potassium in an attempt to determine if this symptom was related to temporary electrolyte imbalance. Evidences of objective improvement were an 18 lb. weight loss, disappearance of rales in the lungs, diminished distention of neck veins, decrease in the size of the liver, and disappearance of orthopnea and paroxysmal nocturnal dyspnea. His pulse rate decreased from 85 per minute to 68 per minute. The pulse rate after a standard exercise declined from 144 to 120, and, finally, to 90. The venous pressure diminished from 165 mm. of saline to 75 mm. Vital capacity increased from 2.8 liters to 3.2 liters. There was no other change in his regimen from that maintained prior to admission. He was put on a maintenance dose of 1.5 mg. of gitalin for five days, and no toxicity developed prior to discharge.

Comment.—This illustrates the enormous requirement of digitalis in some patients, which cannot be appreciated unless the drug is pushed. The presence of the nausea and black spots, present prior to admission, were shown to be unrelated to digitalis intoxication. The amount of digitalis required to produce optimal slowing of his pulse was about 85% of that of the toxic dose, illustrating the narrow margin between the therapeutic effectiveness and toxicity seen in some patients.

Case 3.—A 40-year-old white man had a history of rheumatic fever at the age of 21. He had had congestive failure for three years. At that time he was digitalized and maintained on 0.1 gm. of digitalis leaf per day. Physical examination revealed a pulse of 60 per minute, which increased to 80 per minute after exercise. Blood pressure was 140/90 mm. Hg. Examination of the heart revealed a P. M. I. 1 cm. lateral to the midclavicular line and tapping in quality. M_1 was greater than M_2 and split. P_2 was greater than A_2 and split. There was a Grade 2 systolic murmur at the apex, a Grade 2-3 prolonged apical diastolic rumble, and a Grade 2 blowing diastolic murmur in the second and third left interspaces. The remainder of the examination was negative.

The patient was pushed on digitalis as an outpatient. For two weeks he was given 1.5 mg. per day. At the end of that time his pulse had decreased to 48 per minute at rest and between 65 and 70 per minute after exercise and remained at that rate for the next two weeks of the study. He was then given 2.0 mg. per day for one week, without development of toxicity, and after 2.5 mg. per day for four days he developed anorexia and nausea with no ECG changes. His total dose was 20 mg. above a maintenance of 1.0 mg. per

day, or 7.5 mg., assuming a maintenance dose of 1.5 mg. per day. The anorexia lasted less than one day. Objective evidences of improvement were a venous pressure decrease from 120 to 80 mm. of saline, vital capacity increased from 3.0 to 3.2 liters, and circulation time decreased from 24 seconds to 20 seconds. There was no other change made in his regimen.

Later, he was admitted to the hospital and cardiac catheterization was done. On the basis of this evaluation, surgery was recommended and he was sent out for six weeks on anticoagulants prior to valvulotomy. However, he was placed on only 0.1 gm. of digitalis leaf per day as a maintenance dose. When he returned to the hospital, he had a pulse rate of 70 to 80 per minute and was thought by the house staff to be adequately digitalized. However, on the morning when operation was planned, he was given premedication of atropine, 1/150 grain (0.43 mg.), and his pulse rate rose to 140 per minute. He was then transferred to the Medical Service, and digitalis was augmented. After this, valvulotomy was performed without complication.

Comment.—This patient's bradycardia occurred well before digitalis intoxication. The failure to appreciate the requirements of some patients for digitalis, and subsequent underestimation of the degree of digitalization, may lead to untoward results.

CASE 4.—A man with a 12-year history of coronary disease, angina, and two myocardial infarctions, had developed congestive failure following "pneumonitis" two months before referral. At that time, he was digitalized and maintained on 0.5 mg. of gitalin per day. He had also been taking quinidine, chlorothiazide, meralluride, and anticoagulants. Two weeks prior to admission his gitalin was stopped because of loss of appetite and bigeminy; it was restarted 10 days later on a dose of 0.5 mg. per day. His appetite remained only fair, and his cardiac irregularity persisted. On admission his pulse rate was 84 per minute, with bigeminy. Blood pressure was 105/70; respirations, 20. The patent appeared thin and chronically ill. Pulsatile distended neck veins were seen at 45 degrees. There were bilateral crepitant rales in the lungs. The liver was down 2 fingerbreadths and nontender. Examination of the heart revealed a prominent P. M. I. at the midclavicular line. P_2 was louder than A_2. There was a fairly well-localized Grade 2-3 apical systolic murmur not increased on inspiration and an inconsistent apical diastolic gallop. A second systolic murmur, loudest at the left lower parasternal area, transmitted to the right and increased by inspiration, was also noted. He was thought to have mild digitalis intoxication on admission, and digitalis was omitted for three days. After that time, gitalin was pushed, and he received 7.5 mg. over the next five days, or 2.5 to 5 mg. above a maintenance dose, before anorexia and nausea appeared. Both were gone by the next morning. He lost 12 lb., and his murmur of tricuspid insufficiency disappeared. He was also receiving acetazolamide and mercaptomerin (Thiomerin).

Comment.—Anorexia and nausea in patients with congestive heart failure on digitalis may be due to causes other than excessive digitalis. This may result in the physician's failing to obtain maximal benefit from digitalis. Among these other causes are hepatic congestion, as in this case, in which situation the liver will usually be tender, a finding seldom seen in patients with digitalis intoxication. Other causes for nausea and vomiting in these patients are concomitant unsuspected uremia or drugs such as ammonium chloride, aminophylline, or morphine.

CASE 5.—A 38-year-old white woman with a 30-year history of rheumatic fever had congestive failure for 18 years and had been on digitalis for four years. She entered the hospital with a 10-day history of "flu," with cough, and a three-day history of increased dyspnea, weakness, edema, and nausea. Blood pressure was 96/70 mm. Hg; she had auricular fibrillation at a rate of 96 to 110, and there were wheezes and inspiratory and expiratory rales bilaterally in both lung fields. The heart was enlarged, with a heaving precordial impulse. Murmurs of mitral stenosis, aortic insufficiency and possibly mitral insufficiency, and aortic stenosis were heard. The liver was felt down 2 fingerbreadths and was tender. There was minimal ankle edema.

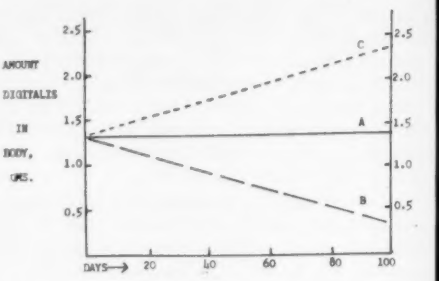
While in the hospital she had frequent episodes of chest pain followed by nausea and vomiting and on one occasion associated with hemoptysis. A diagnosis of pulmonary emboli was made, and she was started on anticoagulants, and given concentrated opium (Pantopon) or dihydromorphinone (Dilaudid) for pain. Because of nausea and vomiting, her physician stopped digitalis, and over a two-week period her congestive failure became progressively severer. At that time, she was seen by a consultant who advised redigitalization, and this resulted in striking clinical improvement. The frequency of the chest pains gradually subsided; signs and symptoms of congestive failure disappeared, and she was discharged from the hospital free of symptoms. Three months later, she was admitted to the hospital with sudden onset of right upper quadrant pain, nausea and vomiting, and a right upper quadrant mass. At operation she was

found to have two large bilirubin stones, hemorrhagic cholelithiasis, and narrowing of the common duct.

Comment.—This patient represents another example of nausea and vomiting from causes other than digitalis intoxication, resulting in discontinuation of digitalis by the physician with potentially serious consequences. It cannot be determined for certain whether her nausea and vomiting were due to pulmonary infarction and congestive heart failure, narcotics, cholecystitis and cholelithiasis, or a combination of these factors.

Comment

One of the commonest causes of "refractory" congestive heart failure is the inadequate use of digitalis. This is probably related to the increasing recognition of digitalis intoxication in recent years. There is fear of using the drug optimally in situations in which gastrointestinal symptoms and cardiac irregularities are due to the basic heart disease or are the result of other forms of treatment. However, a commoner cause of inadequate doses is the assumption that a patient receiving what is thought to be an average maintenance dose will necessarily remain well digitalized. Friedman [4] found a renal excretion of 32μg. to 44μg. of digitoxin per day, increasing to a maximum of 100μg. with larger doses. He found the maximal capacity for destruction to be 50μg. per day. On the other hand, there is some evidence from the work of Okita [5] that the excretion of digitalis decreases when the total amount in the body decreases. It is not known if the destruction of digitalis within the body is similarly reduced or what level of digitalization is necessary for such adjustments to occur in the presence of inadequate digitalis intake. It is unlikely that they occur in the presence of a therapeutic level of digitalization. In any case, there is a large individual variation, and it is apparent that unless the exact maintenance dose for the person is arrived at there may be a gradual accumulation with eventual digitalis intoxication, or a gradual decrease so that there is loss of therapeutic effectiveness and perhaps even complete loss of digitalization. This concept is illustrated in the Figure.



	PATIENT A	PATIENT B	PATIENT C
ASSUMED DAILY EXCRETION	.05	.055	.045
ASSUMED DAILY DESTRUCTION	.05	.055	.045
TOTAL DAILY LOSS	1.0	.11	.09
NET DAILY LOSS OR GAIN	0	.01 LOSS	.01 GAIN
AMOUNT IN BODY AFTER 100 DAYS	1.4	0.4	2.4
RESULT AFTER 100 DAYS	OPTIMALLY DIGITALIZED	UNDIGITALIZED	DIGITALIS INTOXICATION

This is a purely hypothetical illustration of what is probably a general principle of digitalis therapy. The assumptions involved are (1) that all three patients are optimally digitalized with an initial dose of 1.4 gm.; (2) that the total dissipation is slightly different in the three subjects, and (3) that this dissipation remains constant regardless of the amount of the drug in the body. The third assumption is almost certainly incorrect. Hence, a more accurate representation would require curved lines for *B* (convex below) and *C* (convex above). However, this does not invalidate the general concept, and for the sake of simplicity straight lines are drawn. If the principle involved is correct it is clear why a standard maintenance dose continued for a long period will frequently result in escape from digitalis effect or cause intoxication.

Batterman [6] reported that when patients received a maintenance dose of 0.1 gm. of digitalis per day 65% remained adequately digitalized and 10% developed digitalis intoxication. The present study does not clarify the incidence of partial or complete loss of digitalization which occurs. However, it does indicate that patients assumed to be adequately digitalized are frequently able to take large additional doses, and in a number of these patients it can be shown

that inadequate digitalis was the cause of failure to achieve optimal compensation.

We believe that in addition to the initial digitalization and to the use of maintenance dosage, the patient should receive augmentation doses to the point of minor toxicity at periodic intervals. This should not be done (1) when there are no signs or symptoms of congestive failure; (2) when there is evidence of recent myocardial infarction, active carditis, or other acute illness which might make the patient unusually sensitive to digitalis intoxication, or (3) when it has been previously determined by augmentation of digitalis after a period of maintenance that the maintenance dose of the particular patient is neither too much nor too little for optimal digitalization.

This process of augmentation of digitalization when carefully done appears to be safe and not psychologically unpleasant for the patient. However, it does require more time and effort on the part of the physician and more cooperation from the patient. The incidence for cardiac toxicity found in this series is much less than in previously published reports, even those using the same drug and pushing to evidence of minor toxicity.[7] Some possible reasons for this are the education of the patient to take the drug after meals and only provided the appetite has been normal, as well as to watch for other toxic symptoms, careful observation by the physician at least once a day, supplemental potassium chloride, and stopping the drug as soon as a clear-cut end-point is reached. However, it is possible that the low incidence of cardiotoxicity may be related in part to the omission from the study of patients with acute cardiac disorders.

Gitalin was used for the augmentation of these patients because of its short-acting qualities which result in the rapid disappearance of toxicity once it develops. We know no reason why other short-acting preparations would not be equally useful. No attempt was made to evaluate the ratio of therapeutic to toxic dosage; however, in several patients in whom the rate in auricular fibrillation could be used as evidence of optimal digitalis effect, the ratio apparently varied widely, being as much as 85% in some instances, and probably reflected the stage of heart disease. The variability of the dose required to produce toxicity is perhaps a reflection of the short action and variability and excretion of the drug but probably also reflects the individual variations in tolerance and in the need for digitalis among different patients.

Summary

The effects of administering a short-acting digitalis (gitalin) to the point of minor toxic manifestations have been studied in 33 patients with congestive failure. Of these, 18 had been treated by others according to the accepted method of initial digitalization plus standard maintenance dosage with various preparations. All 18 were supposedly optimally digitalized and were referred because of refractory heart failure. It was found that these persons were actually underdigitalized, and most of them were able to take within a few days one-half to two of the usual full digitalization doses before minor toxic symptoms developed. All of them exhibited subjective improvement, and 11 exhibited undoubted objective evidence. In 7 of these 11 the improvement was apparently due to digitalis alone.

These observations indicated that the current standard methods of administering digitalis are inadequate and that periodic augmentation is desirable in patients who are having symptoms despite receiving the drug in the usual accepted maintenance dose. For such augmentation a short-acting digitalis is to be preferred because of the brief duration of such minor toxic effects as are produced.

For the most desirable results certain precautions should be observed during periods of augmentation: (*a*) The patient should take the drug himself and only after meals and provided the appetite shows no sudden decrease. (*b*) During the period of

increased dosage the patient should be seen at least once daily by a physician. (*c*) Potassium chloride should be administered with each dose of digitalis during the supplementary period. (*d*) A clear distinction should be made between anorexia and nausea due to digitalis and such symptoms resulting either from abdominal congestion (which is usually an indication for more digitalis) or from concurrent disease, such as uremia, or from such drugs as ammonium chloride, morphine or aminophyllin. (*e*) It should be recalled that premature beats are frequently due to the underlying cardiac disorder per se and that under such circumstances they may be abolished by digitalis. Rarely, this is true for bigeminal rhythm.

Of 33 patients in whom the drug was administered to the point of minimal untoward effect, three-fourths developed gastrointestinal manifestations without cardiac toxicity. In only three was the reverse observed. No serious toxic effects were encountered.

It is suggested that periodic augmentation of digitalis dosage be employed, with the safeguards mentioned, in patients who are failing to exhibit satisfactory control of congestive heart failure.

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Serum Aldolase in Muscle Disease

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In recent years, progress has been made in the clinical description and delineation of neuromuscular diseases manifest primarily by skeletal muscle weakness. However, accurate diagnosis in the early stages before the development of advanced muscle involvement is still difficult. It is now recognized that a well-rounded symptomatic treatment program can help in preventing unnecessary complications and in obtaining maximal function from the residual musculature. Such a program will be most effective if efforts are directed early in the disease not only toward physical therapy and orthopedic modalities but also toward the psychologic reactions of these patients.[1] There is a need for laboratory assistance not only in diagnosis but for long-term management as an aid in establishment of prognosis, evaluation of therapeutic effects, and as a guide in setting reasonable goals. Laboratory tests, which have been used in the past, such as urinary creatine and creatinine, reflect the amount of past muscle disease and give no indication whether muscle degeneration is actively occurring at the time of the test. In addition, these laboratory procedures lack specificity, since they do not distinguish between the various causes of reduced muscle mass.[2] Muscle biopsy, although helpful diagnostically, does not lend itself to repetitive usage in assaying continued disease activity.

The serum aldolase test seems to offer a new parameter in the evaluation of muscle disease. It probably indicates the presence of muscle degeneration and is thus representative of current disease activity. It is, also, a definite aid in distinguishing primary myopathy from secondary or neurogenic muscle atrophy.

The earliest report on serum aldolase in muscle disease was that of Schapira, Dreyfus et al.,[3-5] following the incidental finding of hyperaldolasemia in two cases of progressive muscular dystrophy by Sibley and Lehiniger, in 1948.[6] It is of interest to note that this finding had been previously reported by Warburg and Christian, in 1943.[7]

This paper deals with the application of serum aldolase determinations to the diagnosis and treatment of muscle and neurological diseases manifest primarily by muscle weakness and atrophy.

Methods

In this work, the method of assay for the serum aldolase was essentially that of Sibley and Lehiniger,[8] as modified by Cook and Dounce.[9] The activity of serum aldolase is reported in micrograms of alkali-labile phosphorus liberated per minute per reaction mixture (2.5 cc.) per milliliter of serum. These values so obtained are comparable to the earliest reported work of Schapira et al.[4-6] All blood samples were centrifuged and the serum stored at −20 C within two hours after venipuncture. It was found that practically all sera were stable for two weeks under these conditions, but some showed appreciable decreases in activity after a month of storage.

Serum phosphohexoseisomerase was determined by the method of Bodansky[10] at 37 C with use of glucose-6-phosphate as substrate and measurement of the appearance of fructose-6-phosphate by the method of Roe.[11] The activity of this enzyme is reported in micrograms of fructose-6-phosphate formed per minute per milliliter of serum per reaction mixture (3 cc.).

Creatine and creatinine were determined on aliquots of 24-hour urine samples by the method of Clark and Thompson[12] and Anker.[13] Muscle biopsy specimens were taken from the rectus abdominis under general anesthesia by members of the Department of Surgery at University Hospitals

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From the Department of Medicine, Western Reserve University School of Medicine.

of Cleveland. Pathological description and diagnosis of the biopsied muscle was done by Dr. Lowell Lapham, neuropathologist, Institute of Pathology, Western Reserve University.

Myosin was extracted according to the Hasselbach and Schneider[14] modification of the classic myosin-extraction technique. Extraction was done in the cold (4 C) during two periods of one hour each.

Because of the need for an objective quantitative method of following the progression of the muscular weakness in muscular dystrophy patients, a means of estimating the muscle strength-mass of an individual patient was adopted. An experienced physical therapist evaluated the strength of the various muscles and muscle groups, using the standard method of manual muscle testing which utilizes gravity and resistance as the criteria for grading muscles.[15] To eliminate individual grading variations among therapists, the same physical therapist did all of the muscle testing referred to in this report.

Each muscle or muscle group was graded on a numerical scale, with 0 as the lowest (no contraction) and 10 as the highest value (normal). In order to arrive at a figure that would indicate the relative mass as well as the strength of the muscle, the numerical value was multiplied by a factor rating ranging from 1 to 4. The standard muscle of unit one was the anterior tibial. These factors are considered to remain relatively constant, even with generalized atrophy. In this manner, a more realistic comparison of muscle strength is obtained, since the standard method of recording manual muscle tests does not give a quantitative evaluation of muscle mass. Thus, 50% degeneration of a large muscle group contributes more weakness to the person than the same per cent degeneration of a small muscle group. The method of factoring was adapted from the work done to standardize muscle testing in the early poliomyelitis patient for γ-globulin and polio vaccine field trials.[16] For the specific purposes of this study, the quantitative comparison was limited to 22 major muscles of the trunk and extremities which were considered to be a representative sampling of the functional involvement in muscular dystrophy patients. On this basis, a total score of 700 is the maximum that could be achieved by a person who rated "normal" for each muscle tested.

There are deficiencies in this as in all techniques of assessing muscle strength-mass. However, carefully done manual muscle testing provides an accurate semiquantitative method of estimating the total muscle strength in the individual patient. This helps more accurately to categorize the extent of muscle degeneration and allows a comparison of residual muscle strength in different patients.

Another system of grading based on functional capacity has been used because it provides a simple and accurate method of assessing over-all muscle performance. It represents a modification of a previously published functional classification.[17] It is less precise than the determination of muscle strength-mass but it is very useful and is probably more accurate than rough clinical estimates of muscle function which have been used previously. A limitation of this grading scheme is that it reflects principally the strength of the lower extremity, trunk, and pelvic musculature as manifest by ambulation and elevation activities. However, this relative defect is minimized in muscular dystrophy because muscle atrophy is genetically determined. There is, therefore, a proportional loss of upper extremity strength concomitant with lower extremity weakness.[18] Premature confinement to braces or wheel chair makes this grading system less valid because of disuse atrophy. Patients are graded on a scale of 1 through 11, with the higher classifications representing progressively severer involvement. The criteria for functional classification:

(1) Minor degrees of muscle weakness manifest by retarded walking age in children, tendency to stumble and fall, inability to run, poor coordination, etc.
(2) Obvious defect in posture and walking stance but walks and climbs stairs without assistance.
(3) Walks but climbs steps only with aid of railing.
(4) Walks but climbs eight standard steps with aid of railing in over 25 seconds.
(5) Walks but cannot climb steps.
(6) Walks unassisted but cannot climb steps or get out of chair.
(7) Walks only with assistance of braces.
(8) In wheel chair. Sits erect, can roll chair and perform bed or chair activities of daily living.
(9) In wheel chair. Sits erect, unable to perform bed and chair activities without assistance.
(10) In wheel chair. Sits erect only with support. Able to do only minimal activities of daily living.
(11) In bed, can do no activities of daily living without assistance.

Results

Controls

The control group for this study included 73 persons among whom there were 19 normal adults and 54 hospitalized persons; the latter group had many different diseases. The only criterion for the control group was the absence of muscle weakness or loss of muscle mass or other nonloco-

motor diseases that have been shown in previous papers occasionally to elevate serum aldolase. The average value for serum aldolase in the control group is 0.39 units, and the mean is approximately 0.35 units. The standard deviation was 0.15 units. Two standard deviations above average is essentially 0.7 units, which was considered the upper limit of normal for this work. One control determination exceeded 0.7 units but was included despite an extensive dermatitis, which might have elevated serum aldolase because of tissue destruction.

The distribution of control values does not fall into a perfect bell-shaped curve that would be expected for a normal population. The largest number of values fall between 0.3 and 0.4 units. There is a slight nonsignificant difference between the average values for adults and children and between males and females. Four authors have found no significant difference in serum aldolase values among these age and sex groups,[19-22] whereas Schapira et al.,[5] found the enzyme values for children to be slightly higher than for adults. There is only one report of a difference in serum levels between males and females in previous studies on aldolase and other serum enzymes.[23-27]

Muscular Dystrophy

This study includes a series of 52 cases of progressive muscular dystrophy. The diagnosis was based on the clinical picture and muscle biopsy specimens. There were 31 persons 15 years of age or younger and 21 over 15 years. The children under age 15 with progressive muscular dystrophy showed almost universal elevation of serum aldolase. The older group with dystrophy had a much smaller incidence of hyperaldolasemia, with only one-third of values being above normal limits. The average value for the children under age 15 was 3.7 units, and the average value for the older group was 0.63 units. Only two children had normal values below 0.7 units, and one of these was a girl (0.5 units). The only boy with normal serum aldolase (0.57 units) was 13 years old. He was one of the most severely involved patients, as indicated by a functional classification of 9 and a total muscle grade of 109, as compared to a normal total muscle grade of 700. Of 21 in the older group, the 14 with serum aldolase levels below 0.7 units were equally divided between males and females (Table 1).

TABLE 1.—*Relationship of Serum Aldolase to Age and Sex in Progressive Muscular Dystrophy*

	Values Above 0.70 Units		Values Within Normal Limits		
Ages	Males	Females	Males	Females	Totals
5-15	28	1	1	1	31
15-70	7	0	7	7	21

Serial aldolase determinations have been obtained on 30 muscular dystrophy patients over periods of 5 to 20 months with an average follow-up of 14 months. Certain trends are evident when aldolase is plotted against time (Fig. 1). Young patients (ages 3-15) usually have high aldolase values with a tendency for wide variation in the height of the serum levels; but in spite of the variation, the serum aldolase practically never drops to within normal limits within the period of study. The older patients have lower values, which show relatively slight fluctuations. Values for the younger patients do not show decreasing levels with time as previously suggested.[20]

The level of serum aldolase in muscular dystrophy decreases inversely with age (Fig. 2). However, there are other chang-

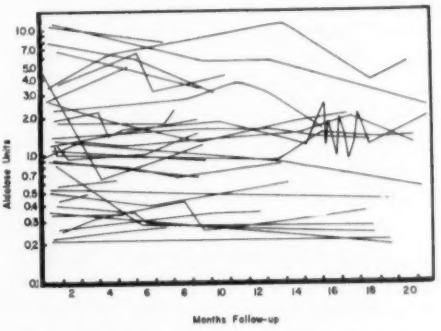

Fig. 1.—Serial aldolase determinations in patients with progressive muscular dystrophy.

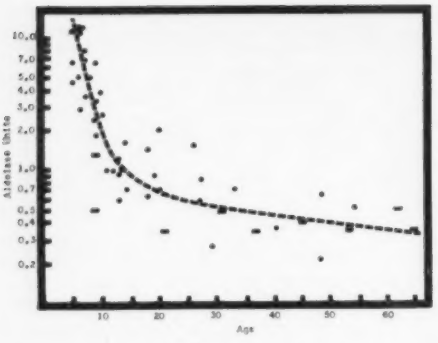

Figure 2

Fig. 2.—Relationship of age to serum aldolase in progressive muscular dystrophy. Dots represent males; dashes, females.

Fig. 3.—Relationship of serum aldolase to myosin coefficient (milligrams of myosin nitrogen per 100 mg. noncollagenous nitrogen per pound body weight) in progressive muscular dystrophy.

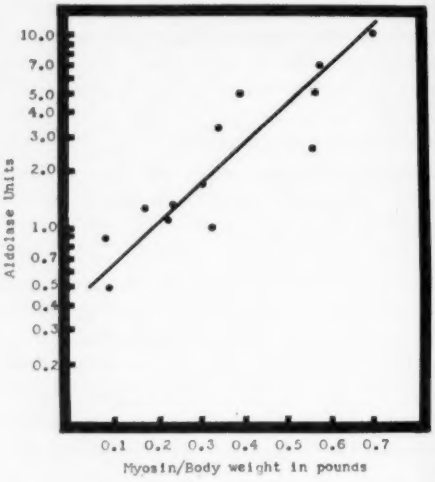

Figure 3

ing factors as the patient ages. One such factor is the decrease in muscle mass. A direct measure of the residual muscle mass is not possible, but it may be estimated by several procedures. One method is to correlate serum aldolase with creatinine coefficient (urinary excretion of creatinine in milligrams per 24 hours per pound weight). It has long been considered that the total daily urinary excretion of creatinine is directly related to the amount of functional muscle present in the body.[2] No allowance can be made for the differing percentages of total body mass contributed to body weight by differing amounts of fat and connective tissue replacing parenchymal muscle tissue. Despite this limitation, a fair correlation exists between serum aldolase and creatinine coefficient in male muscular dystrophy patients. This indicates that in muscular dystrophy the serum aldolase level is influenced by the amount of muscle present. There is no correlation between the 24-hour creatine excretion or per cent creatinuria with the enzyme level.

Myosin is regarded as the chief contractile protein of skeletal muscle. Measurement of myosin which is representative of parenchymal muscle mass may be used as an assay of the amount of functional skeletal muscle. The myosin content of skeletal muscle has been determined quantitatively by biopsy of the rectus abdominis muscle of a number of muscular dystrophy patients.[29] Determinations for both serum aldolase and myosin content have been done simultaneously on 13 patients. The linear relationship between serum aldolase and myosin content, based on a parenchymal tissue reference base of noncollagenous nitrogen, suggests that higher serum aldolase levels occur in patients having the greatest functional muscle mass as manifest by myosin content (milligrams of myosin nitrogen per 100 mg. of noncollagenous nitrogen) per pound of body weight (Fig. 3). Glycolytic activity[29] in extracts of the same muscles did not show a correlation with aldolase levels.[29]

Two clinical methods have been used for estimation of muscle mass in these patients. The two techniques, described in methods section, are muscle strength-mass, as determined by manual muscle testing and functional grading. Definite correlations can be shown to exist between serum aldolase levels and muscle mass and functional class. Serum aldolase values decrease as the muscle mass decreases and functional classification is fixed at a lower level. As in the previous graph, these are logarithmic relationships. The graph correlating residual

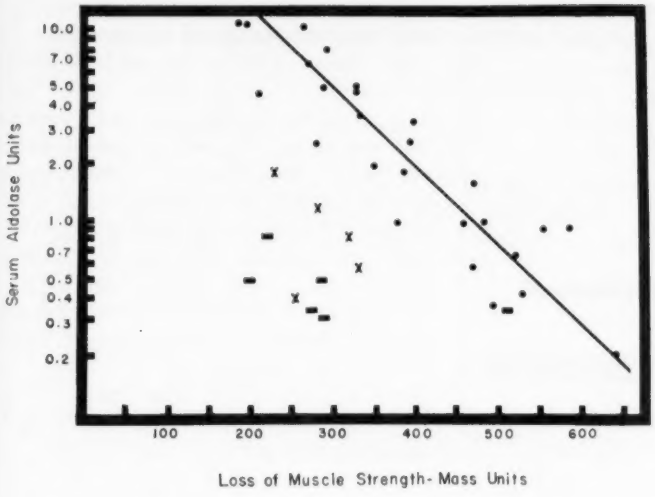

Fig. 4.—Relationship of serum aldolase to loss of muscle mass in progressive muscular dystrophy.

muscle mass with serum aldolase (Fig. 4) indicates that the aldolase level in the females and five of the male patients consistently fall far below the remaining aldolase values. Analysis of this observed difference shows that all these patients had generalized dystrophy of a mild and slowly progressive form and that all the males had the onset of symptoms after the age of 6 years. A plot of functional grade against serum aldolase level shows a similar relationship between decreased functional classification in muscular dystrophy and low serum aldolase.

An important consideration in the management of muscular dystrophy is prognosis. Probably the single most useful prognostic criterion at the time of the initial examination is the age of the patient when symptoms of muscle weakness first appear. Previously, there has been no satisfactory laboratory test which was reliable prognostically at this early date. The urinary creatine excretion is not particularly useful in the initial phase of muscle weakness, since children have physiologic creatinuria. To determine whether serum enzyme determinations may be helpful in prognosis, patients with muscular dystrophy have been followed for an average of 30 months by serial quantitative manual muscle tests and aldolase determinations. There is a positive correlation between the net loss of muscle mass and the enzyme level (Fig. 5). Patients with slight loss of muscle mass over the 30-month period (less than 50 units) tend to have normal or slightly elevated aldolase levels. Conversely, those patients showing rather severe loss of muscle mass over the 30-month period (100-250 units) never show normal enzyme levels and the serum aldolase is almost always markedly elevated. All the females studied fall into the group with low aldolase.

Polymyositis (Dermatomyositis)

Serum aldolase has been studied in 13 persons with "collagen disease" type of

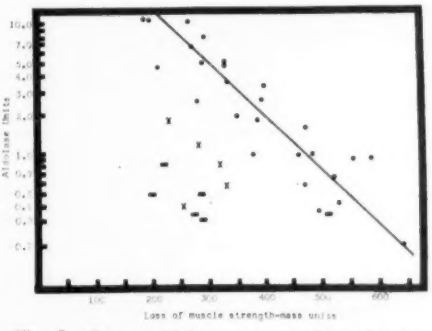

Fig. 5.—Serum aldolase concentration related to the progression of muscle degeneration in dystrophy. Dots indicate males; dashes, females; X, males with disease onset after age 6 years.

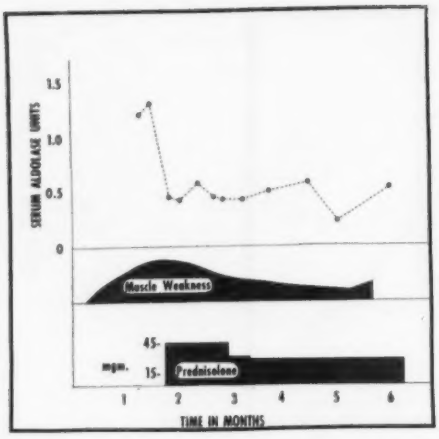

Fig. 6.—The effect of cortisone therapy on the serum aldolase level and muscle weakness in polymyositis in the 45-year-old Negro man reported in the text.

myositis. Dermatomyositis and polymyositis are considered to be essentially the same disease so far as the muscle pathology is concerned. Six of these patients have shown aldolase evaluations above normal, whereas seven were within normal limits. In four of the cases with elevated levels, it was possible to determine serum levels before and after institution of steroid therapy. In each case, after the establishment of adequate steroid dosage serum aldolase values promptly fell to within normal limits. Clinical changes in muscle strength lagged behind the decrease toward normal of serum aldolase values. The relationship of serum aldolase to steroid administration is shown in Figure 7.

Case Summaries

A 12-year-old white boy had a sudden onset of muscle weakness and tenderness. The diagnosis was dermatomyositis. He was placed on an initial dose of 40 mg. prednisone per day and within a week

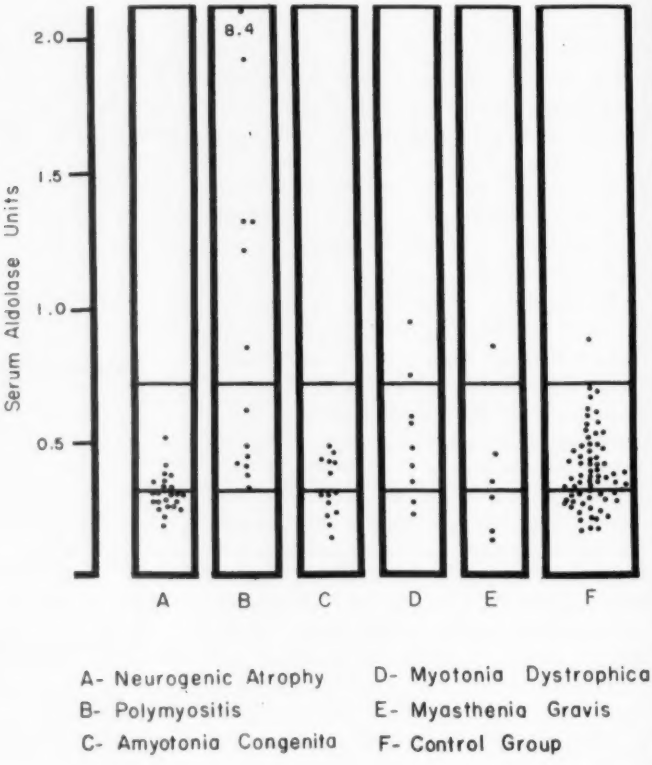

Fig. 7.—Serum aldolase concentration in neuromuscular diseases with skeletal muscle weakness.

showed falling aldolase levels. The improvement of muscle weakness was somewhat slower. He was discharged from the hospital in one and one-half months on 10 mg. per day with almost complete recovery.

A 60-year-old white woman had a slow onset of weakness involving principally the axial musculature. The diagnosis of polymyositis was confirmed by biopsy. The initial steroid therapy was 200 mg. cortisone per day. Serum aldolase gradually fell to within normal limits although there was only minor clinical improvement at that time. After eight months, cortisone therapy was discontinued, and she remains relatively well two and one-half years later.

A 61-year-old Negro man developed muscle weakness over a six-month period and was bedridden prior to institution of steroid therapy. Serum aldolase levels were extremely high and did not show any decrease after 20 days' treatment with 40 mg. of prednisolone per day. The dose was then raised to 70 mg., and subsequently serum aldolase levels gradually fell almost to normal. However, in the third month of steroid therapy, the patient clinically deteriorated and later died of moniliasis. There had been little improvement in muscle strength by manual testing.

A 45-year-old Negro man, one month prior to therapy, developed severe progressive shoulder and hip girdle weakness. This was of such severity that the patient was confined to bed with complete inability to perform any activities of daily living. Following the institution of 45 mg. prednisolone therapy per day the serum aldolase rapidly became normal. Clinical improvement was slower. However, within one month, the man could walk again. Six months later, after marked clinical muscle improvement, the patient died of bronchogenic carcinoma. Serial aldolase values and steroid therapy are plotted in Figure 6.

Determinations have also been made on six cases of lupus erythematosis and two cases of unclassified collagen disease. All were within normal limits.

Miscellaneous Myopathies

Included in this study is a 25-year-old Negro man who has generalized sarcoidosis with proven severe granulomatous muscle involvement. Serial aldolase values during 34 months of follow-up show five peaks, each of which followed a reduction in steroid dosage. At each peak, there was also a concomitant increase in muscle weakness. Both the weakness and elevated serum aldolase responded to increased steroid dosage. The patient at present is well, working, and able to do all activities of daily care.

The incidence of elevated serum aldolase in myotonia dystrophica is low in this series. Nine cases of myotonia dystrophica were studied; only two had elevated values. Of the latter two cases, one had a single elevation 0.92 units and the other had two values of 0.35 and 0.73 units (Fig. 7).

Serum aldolase may be elevated in all of these primary myopathies. However, a normal aldolase level does not exclude the possibility that the disease in point is of the primary myogenic variety.

Neurogenic Atrophy

A variety of diseases with muscular atrophy secondary to involvement of anterior horn cells and peripheral nerves have been studied (Fig. 7). Every case of the 14 with amyotonia congenita studied had normal serum aldolase levels. Eighteen patients with various other progressive neurogenic muscle atrophies, which included cases of amyotrophic lateral sclerosis, peroneal muscular atrophy, Friedreich's ataxia with muscle weakness, and a variety of other neurogenic diseases with muscle weakness, were surveyed. All were within normal limits except for two patients. One man with progressive spinal atrophy had a single borderline elevation of 0.73 units in the middle of a series of nine normal determinations. This occurred following temporary confinement to a wheel chair. There was a transient elevation to 1.0 units at the onset in one of two cases of Guillain-Barré syndrome. One month later, a follow-up determination was 0.43 units. The second case of Guillain-Barré syndrome had normal values.

Defective neuromuscular transmission, as exemplified by myasthenia gravis, usually shows normal aldolase levels. Of six cases, one patient had one elevated value (0.83 units). The determination was made at a time when the previously ambulant patient was confined to bed owing to a recent exacerbation of the disease. Elevations of serum aldolase occurred rarely in patients with neurogenic atrophy or myasthenia gravis. The aldolasemia was transient and was found either at the onset of disease or with acute immobilization.

TABLE 2.—*Summary of Compiled Data on Serum Aldolase and G. O. Transaminase Values in Myopathies and Neuromuscular Diseases*

	Aldolase												Transaminase							
	Elevated					Normal					% Elev.	Elevated			Normal				% Elev.
	A	B	C	D	Tot.	A	B	C	D	Tot.		E	F	Tot.	E	F	Tot.	
Muscular Dystrophy																		
Ages 0-15	29	83	13	15	140	2	5	1	1	9	94	41		41	5		5	90
Ages 15-70	7	21	5	16	49	14	4	11	8	37	57	6		6	35		35	15
Myotonia dystrophica	2	1	1		4	7	5	1		13	24				7		7	0
Polymyositis	6	6	1		13	7		2		9	59	2	6	8	2	4	6	57
Lupus erythematosis		1			1	6				6	14							
Polyarteritis							2			2	0							
Amyotonia congenita						14	11			25	0							
Myasthenia gravis	1				1	5	4	4		13	7	2		2	2	4	6	25
Poliomyelitis			1		1	6	19			25	4				6		6	0
Amyotrophic lat. sclerosis						5	3			8	0				4	3	7	0
Peroneal muscular atrophy						2	2			4	0				1	1	2	0
Guillian-Barré	1				1	1	3			4	20				3	2	5	0
Misc. neurogenic atrophies						11	5			16	0					11	11	0

Literature Survey

Owing to the relatively small number of cases that can be gathered by any one group of investigators, it is helpful to compare the results of previous studies. There have been only two published reports on serum aldolase and two on transaminase in neuromuscular disease.[4,20,28,30] Personal communications from Dr. Carl M. Pearson and Dr. Schapira[31,32] have been included in an attempt to summarize the current cumulative data. From these data in Table 2, it can be seen that of 140 children 15 years old or younger with muscular dystrophy about 94% have elevated serum aldolase values.

However, this high positive correlation does not apply to female children, who often show normal values in this age group. The number of female dystrophic children is small, but they do seem to differ from male children, since only half of the girls have elevated serum aldolase activity. The work of the authors includes two female children, with one showing a high value. The data of Schapira et al. includes nine females, five of whom had values within normal limits. This sex difference is not shown in Table 2. Pearson reported two female children, both of whom had elevated serum levels. If the females are eliminated, the data indicate that in muscular dystrophy 118 of 120 male children, or 98%, can be expected to have elevated aldolase, thus making this test of particular diagnostic importance in male children.

Fifty-seven per cent of the dystrophic adults have elevated aldolase levels. In adults, as in children, women have a lessened incidence of elevated aldolase values; the data of Schapira et al. included eight adult females, six of whom had elevated values; the authors' cases included seven females, all of whom were normal, and Pearson included six females, five of whom were normal. Thus, only about 40% of adult women with dystrophy will have elevated values, as compared to 64% of adult male dystrophics.

Two forms of myopathy that may be confused with muscular dystrophy, especially in the adult, are myotonia dystrophica and polymyositis, both of which may exhibit serum aldolase elevations. Slightly over one-half of the 22 collected cases of polymyositis show increased serum aldolase activity, while about one-quarter of the 17 cases of dystrophica myotonia show high serum aldolase.

The relationship of aldolasemia to neurogenic muscle atrophy is very different. It is evident from the results of all studies that neurologic diseases with muscle weakness show only rare elevations in aldolase values. There were only four high values among 95 patients studied. Aldolase elevations in our cases were transient and occurred only once in a series of determinations. All 25 collected cases of amyotonia congenita had normal serum levels. Our results and the cumulative data from the literature on serum aldolase in the muscle disease show good agreement.

A much smaller group of patients have been studied with use of transaminase assay. The results of the two methods agree very closely, although more adults with muscular dystrophy have shown elevated values by the aldolase method (Table 2). A recent study by White and Hess [33] indicates that there is less transaminase in skeletal muscle than aldolase. This might account for the fewer transaminase elevations in milder forms of muscle degeneration. Aronson and Volk compared aldolase and SGO-transaminase levels. They found no consistent elevations in representative patients with muscular dystrophy and other illnesses. The serum aldolase determination appears to be a slightly more sensitive assay in primary degenerative myopathy than the serum transaminase determination.

Phosphohexoseisomerase Assay

Some work was done in our laboratory with serum phosphohexoseisomerase in the initial phase of this study. The average value for a total of 71 normal persons was 3.9 units. In muscular dystrophy, 15 older patients gave an average of 3.6 units and 8 children below the age of 15 years gave an average of 5.2 units. In general, the results of this enzyme assay paralleled those of aldolase, although a plot of aldolase against phosphohexoseisomerase showed less correlation than expected. Application of this test to a small series of other diseases gave results parallel in general to those of aldolase. Extensive studies were not done with this enzyme assay because the procedure lacked sensitivity and did not seem to offer any additional information not furnished by aldolase studies. This is in agreement with the findings of Schapira.[5]

Nutritional Dystrophy

Early in the work on serum aldolase, it was of interest to know the effect of the nutritional type of dystrophy on the serum aldolase. Nutritional muscular dystrophy due to vitamin E deficiency was produced in a small group of young male white rabbits. The diet prepared by Nutritional Biochemical Company of Cleveland was similar to the diet used by Young and Dinning.[34] Preliminary results showed the average serum aldolase value for 10 control rabbits was 3.7 units. After 12 days on the vitamin E-deficient diet and before any muscular symptoms were observed, the average serum aldolase for six rabbits was 5.5 units. The rise in serum aldolase preceded the appearance of muscle weakness. The onset of dystrophy varied between 20 and 50 days, and in most instances, led to rapid death. Two surviving rabbits with dystrophy were killed. The aldolase values after 48 and 55 days on the diet were 18 and 16 units, respectively, which, when compared to the control average of 3.7 units, represents a significant rise. Histological sections revealed in both cases acute degeneration of muscle with interstitial inflammation. These preliminary experiments suggest that the elevated serum aldolase reflected the degeneration of skeletal muscle tissue.

There is a recent report by Beckman and Buddecke [35] in which vitamin E deficiency was developed in five rats. They, also, found significant elevation in serum aldolase. In addition, they determined aldolase in the muscle and liver. No significant change in enzyme activity was found in the liver, while muscle had increased aldolase activity. These results differ from human muscular dystrophy, where muscle aldolase is decreased. This indicates that nutritional dystrophy may differ basically from human muscular dystrophy.

Comment

In the initial investigations by Schapira et al.,[4,5] it was felt that an increased serum aldolase in cases of muscular weakness was very strong evidence for the diagnosis of progressive muscular dystrophy in contradistinction to normal values found in the various neurogenic muscular atrophies, including acute anterior poliomyelitis, polyradiculoneuritis, amyotrophic lateral sclerosis, peroneal muscular atrophy, and amyotonia congenita. Aronson and Volk [20] found a rare serum aldolase elevation in a few cases of neurogenic atrophy, including poliomyelitis, in one case of amyotonia congenita, and in several cases of Tay-Sachs disease, and twice in upper motor neuron lesions. Pearson [30] reported elevated transaminase in one case of myasthenia gravis. Recently, Aronson and Volk [36] have reported hyperaldolasemia in experimental cauda equina section, neurotomy, and tenotomy in the dog, where it was shown that hyperaldolasemia might continue for as long as 20 weeks or more.

Owing to these conflicting data, uncertainties developed concerning the value of serum aldolase in the differential diagnosis of muscle disease. However, with the accumulation of more data, it appears that the serum aldolase determination as a supplementary laboratory test has a definite role in the differential diagnosis of muscle weakness. The serum aldolase determination is most useful in separating the primary degenerative and inflammatory diseases of muscle from those conditions where muscle is secondarily affected by neurogenic atrophies or diseases of neuromuscular junction block, e. g., myasthenia gravis. The ability to place the patient into one of these two large disease groups enables the clinician to narrow the diagnostic field appreciably. Both the experimental results reported in this paper and the accumulated data summarized in Table 2 indicate that the patient with an elevated serum aldolase will almost always have a primary myopathy. In a boy under 15 years of age, an elevated aldolase is a most significant finding, pointing toward a diagnosis of muscular dystrophy, since enzyme elevation has been demonstrated in 98% of these cases. In the older patients with muscular dystrophy, the incidence of hyperaldolasemia progressively diminished with increasing age. Yet, when there is an elevation in the adult patient, the test is of significance.

The only other common diseases causing muscular weakness with elevated serum aldolase values are polymyositis and dystrophica myotonia. In the adult, a very high aldolase value more often indicates polymyositis than muscular dystrophy due to the infrequency of high serum aldolase in adult muscular dystrophy patients. A further difference between the two diseases is the return of elevated aldolase values to normal levels, which may occur in polymyositis after treatment with steroids. Steroids are ineffective in muscular dystrophy and do not lower the hyperaldolasemia. Serial determinations show hyperaldolasemia in muscular dystrophy is consistently present over long periods of time. Though there may be wide variations in the height of elevation from one determination to the next, dystrophy patients with hyperaldolasemia have almost never returned to normal level during the several years of serial determinations.

The prognostic value of serum enzyme levels in muscular dystrophy has been a matter of dispute. Schapira et al. reported that hyperaldolasemia had no prognostic

value in dystrophy.[5] They based this opinion on high values of serum aldolase in patients not severely affected, with slow evolution of disease, and, conversely, because they found normal enzyme levels in some severely affected patients. Pearson, on the other hand, observed a positive correlation between the rate of the dystrophic process and the enzyme levels.[30] His cases are divided into three groups based on estimated rate of progression. In his series, the more rapid the clinical progress of the disease, the higher the enzyme levels were.

The data reported in this paper support the thesis that helpful guidance in prognosis can be obtained from the serum aldolase. There are, however, many difficulties in the correlation of estimated disease progression and aldolase levels. A primary distinction must be made between the rate of disease progression and the degree of severity of muscle atrophy. These two are independent processes as far as serum aldolase is concerned. Disease progression is a changing dynamic function of muscle, while severity is the net result of past muscle degeneration. Serum aldolase in muscular dystrophy depends upon the extent of the active degeneration, residual muscle mass, and probably many other factors, one of which may be muscle membrane permeability.[37] It is not a direct measure of the extent of the muscle atrophy.

The aldolase levels are low when there has been appreciable loss of functional muscle mass and with increasing age regardless of the immediate rate of disease progression. The far-advanced dystrophic, with little residual muscle mass, will show a low aldolase, while the younger patient with relatively good preservation of muscle mass but with active muscle degeneration will have high aldolase. The rate of measurable muscle loss does not proceed as a straight-line function but has a decreasing slope after substantial muscle mass decrement has occurred. An average of serial aldolase levels probably reflects the mass of muscle activity undergoing degeneration, but there may be marked day-to-day variation in enzyme levels because of changes in the degree of acute muscle degeneration. However, at present, very short-term variation in disease intensity cannot be detected clinically.

The clinical rate of progression in muscular dystrophy is best estimated by serial muscle tests, functional tests of performance, and determination of the urinary creatine and creatinine excretion. However, these measurements may be appreciably influenced by psychologic and physical factors which decrease muscle function nonspecifically. Thus, patients show a striking change in functional status when they lose the power of independent ambulation. This apparent manifestation of disease progress may be due largely to psychologic factors and may occur without any immediate loss of muscle substance. In such cases, nonspecific disuse atrophy supervenes and the patient will then show decreased muscle strength on testing. This is very different from the loss of muscle mass which occurs as a direct consequence of dystrophic muscle breakdown.

Because of the generally poor prognosis in muscular dystrophy, it is important to be able to select those patients who will show the least physical regression. Rehabilitation goals requiring better maintenance of muscle function can be higher in these patients. The dystrophic patients with the best prognosis fall into two groups. The first is composed of females. Here age does not seem to be correlated with enzyme levels or rate of progression. All the females have low or normal enzyme levels and have done relatively well. The other group of patients, who did better than average, were males over the age of 15. This group of patients tends to have relatively lower enzyme levels than the younger dystrophics under 15 years. Therefore, the age and sex of the dystrophic patient are the most important prognostic factors, and this difference in prognosis is reflected in the degree of aldolasemia.

Myotonia dystrophica may be regarded as a form of primary myopathy. However,

the aldolase elevations in this disease are both minimal and inconsistent, and so serum enzymes are generally of little aid in diagnosis. Aldolase determinations will be helpful when elevated, but in this disease normal levels are found more often.

Neurological diseases with secondary muscular atrophy seldom show elevated enzyme levels, and when this does occur, it is only a borderline transient elevation that can usually be related to severe acute atrophy either at onset of disease or with a temporary exacerbation after the process has already been established. There was no apparent relationship between the severity of the muscle atrophy and wasting in neurogenic atrophy and the serum aldolase level. Not only were the muscles of many of these patients more severely wasted than similar cases of primary myopathy, but also the loss of muscle mass was taking place at a faster rate. Yet, the clinical deterioration was never manifest by elevated serum aldolase levels. This suggests that the basic metabolic processes in the muscle may be very different in the two diseases, despite the stereotyped clinical muscle weakness seen in both types of muscle disease. Serial determinations will help distinguish the transient serum aldolase elevations seen occasionally in neurogenic atrophy from the persistent elevations in the primary myopathies. From these data, it can be stated that elevated serum aldolase is generally an indication of primary myopathy when muscular weakness is the principal symptom.

The enzyme assay may prove useful in the diagnosis of early cases of dystrophy, where the characteristic pattern of muscle weakness and altered posture have not occurred. Data are lacking as to the time of onset of hyperaldolasemia in the muscular dystrophy child. If one assumes that it is present from birth or shortly after, it might be possible to diagnose muscular dystrophy in the infant whose only symptom is retarded walking. This information as to date of onset might be obtained by following new male babies in known muscular dystrophy families. Since age correlations indicate that aldolase is highest in youngest patients with dystrophy, the chance of finding hyperaldolasemia in children affected with muscular dystrophy should be excellent. Conversely, a normal serum aldolase in a male child suspected of muscular dystrophy is strong evidence against diagnosis. Several young boys have now been seen who were muscular dystrophy suspects because of family history of dystrophy and questionable slowness in motor activities. A normal serum aldolase is very helpful in ruling out early muscular dystrophy in these children. In this age group, creatinuria is a usual finding, and clinical muscle testing is often not satisfactory due to poor cooperation.

A problem in polymyositis (dermatomyositis) has been the lack of a satisfactory laboratory test which would assist the clinician in diagnosis, prognosis, and determination of optimum therapeutic schedules for steroid administration. The determination of urinary creatine and creatinine has been suggested for these purposes. However, creatinuria in dermatomyositis has been found to be an extremely variable phenomenon. Christianson and O'Leary,[38] after reviewing their experience in dermatomyositis, concluded that the determination of urinary creatine and creatinine is of questionable value in the diagnosis and prognosis of dermatomyositis.

An elevated serum aldolase appears to offer valuable assistance in the diagnosis of polymyositis when interpreted in light of clinical findings. Aldolase determinations give additional assistance in regulating steroid therapy in this disease. It appears that chemical changes in the muscle as evidenced by change in aldolase blood levels precede clinically demonstrable changes is muscle strength. The enzyme level, therefore, reflects more accurately than muscle testing this immediate response to steroid therapy. Because of the lack of a laboratory guide, such as serum aldolase, steroid therapy for polymyositis has been largely empirical in the past. The suggested treatment schedules have varied widely not only

in terms of maximum initial dosage of steroid but also in the duration of therapy and in the speed at which the drug dosage was tapered. It appears likely that the lack of an objective sensitive guide for therapeutic evaluation may have resulted in too little steroid being given initially in certain instances, and in other cases the daily dose level may often have been tapered too quickly. Therefore, the lack of significant clinical response in certain patients may have been due to inadequate dosage. The clinical course of patients with inflammatory muscle disease, reported in this paper, indicates that steroid therapy can be titrated accurately with serum aldolase determinations. This allows individualization of treatment schedules. It should not be necessary to depend on the slow clinical improvement in muscle strength for guidance in regulating steroid therapy. This should help avoid not only the too low initial steroid schedules but also, conversely, unnecessarily prolonged high dosage with increased danger of cortisone-induced complications. These dangers are especially troublesome in the management of the older patients with polymyositis.

Serial serum aldolase determinations, also, offer promise as a laboratory aide in evaluating future forms of treatment for other primary myopathies. The presence of uniformly high serum aldolase levels in juvenile muscular dystrophy means that any new form of therapy for this disease could easily be assayed in almost all patients by the aldolase determination.

Summary

Serum aldolase has been determined in a series of patients with neuromuscular diseases manifested primarily by skeletal muscle weakness.

The serum concentration of aldolase was elevated in cases of primary myopathy. This included degenerative and inflammatory muscle disease, such as polymyositis, muscular dystrophy, and dystrophica myotonia. The highest serum enzyme levels occur in polymyositis and in juvenile muscular dystrophy. The aldolasemia in muscular dystrophy is diminished with increasing age, diminished muscle mass, and decreased functional ability.

Enzyme levels appear to have prognostic value in dystrophy, since there is a positive correlation between net loss of muscle mass and serum enzyme concentration.

Patients with muscle weakness due to neurogenic atrophy or neuromuscular junction block have a normal serum aldolase. This is a helpful differential diagnostic aid in separating these cases from the primary myopathies.

Aldolase determinations may give valuable assistance in regulating steroid therapy in polymyositis. Biochemical changes in muscle as reflected by decrease in aldolase blood levels precede clinically demonstrable improvement in muscle strength.

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Common Duct Stone Producing Charcot's Hepatic Fever Without Jaundice

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Illnesses characterized by recurring attacks of fever often constitute baffling diagnostic problems. In the differential diagnosis of such illnesses one usually includes the intermittent fever associated with obstruction of the common bile duct. A history characteristic of biliary colic or the presence of clinically detectable jaundice in such patients considerably lessens one's diagnostic difficulties. Charcot's fever unassociated with such focalizing signs or symptoms can represent an enigma.

We recently encountered three patients whose fevers were associated with stones in the common bile duct. These patients did not have clinically detectable jaundice, nor did they give a history diagnostic of biliary colic. Because of the interest in Charcot's fever generated among us who participated in the care of these patients, we examined the files of the Mayo Clinic for the five-year period, 1951 to 1955, inclusive, in search of similar cases. All cases of choledocholithiasis found at operation or necropsy during that period were reviewed. If in addition to a stone in the common duct any condition such as stricture of the bile duct or carcinoma of the pancreas also existed, the case was eliminated. Of a total of 1,063 cases of choledocholithiasis studied 3 met our criteria. It is the purpose of this paper to report the three cases recently encountered and the three additional cases found in searching the records.

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Report of Cases

CASE 1.—A 66-year-old man came to the Mayo Clinic on Nov. 14, 1956, because of recurrent fever and shaking chills of four months' duration. The oral temperature was said to have reached 105 F and to have recurred at intervals of 24 to 36 hours. Characteristically the fever and chills occurred between 4 and 8 p. m. daily. The fever was preceded by generalized myalgia, which increased as the temperature rose and disappeared as it receded. At no time had he had any abdominal pain. He had lost 15 lb. In November, 1950, he had undergone cholecystectomy elsewhere, at which time several stones were found, but the common duct had appeared normal and had not been explored.

Physical examination revealed an elderly man who did not appear ill. The only significant physical findings were an oral temperature of 100 F, a nontender liver palpable 1 cm. below the right costal margin, and the absence of the patellar and Achilles reflexes. The patient was not visibly jaundiced.

The results of laboratory examination were as follows: urinalysis, negative; hemoglobin, 14 gm. per 100 cc. of blood; erythrocytes, 3,300,000, and leukocytes, 4,200 per cubic millimeter of blood; differential count of leukocytes, normal; erythrocytic sedimentation rate, 41 mm. in 1 hour (Westergren method); serum proteins, 6.7 gm. per 100 cc., and albumin-globulin ratio, 4.4:2.3; direct-reacting serum bilirubin, 0.6 mg., and indirect-reacting bilirubin, 0.6 mg.; retention of sulfobromophthalein in the serum after intravenous injection of 5 mg. of dye per kilogram of body weight, 34%; cholesterol, 200 mg., and total lipids, 549 mg. per 100 cc. of plasma; thymol turbidity test of hepatic function, 1 unit; zinc sulfate turbidity test of hepatic function, 15 units; prothrombin time, 18 seconds; serum alkaline phosphatase, 160 units per 100 cc. (King and Armstrong method), and cephalin-cholesterol flocculation test, negative. Three blood cultures gave negative results.

Roentgenograms of the thorax did not disclose any abnormality. Cholangiographic examination with the aid of intravenously injected dye was attempted, but no dye appeared in the biliary tract.

At operation, on Nov. 20, 1956, the liver appeared grossly normal. The common bile duct was thin-

walled and enlarged to a diameter of about 3.5 cm. A large stone was found impacted in the ampulla of Vater. The postoperative course of the patient was without complication, and his temperature remained within normal limits.

The fact that this patient had previously undergone cholecystectomy for cholelithiasis, currently had slight increase of the serum bilirubin and marked increase of serum alkaline phosphatase, retained sulfobromophthalein in his serum at the end of one hour, and failed to excrete radiopaque material into his biliary tract led to the suspicion of choledocholithiasis despite absence of abdominal pain and of visible jaundice. The patient wrote on Jan. 27, 1958, that he had had no recurrence of fever or other manifestations of biliary disease since his operation.

CASE 2.—A 69-year-old woman was admitted to the clinic on Oct. 1, 1957. In mid-February, 1957, she had had chills and fever for one week, which had abated after treatment with penicillin. In August, 1957, she again had fever, along with vomiting, for which she received penicillin, and the complaints had promptly subsided. However, one week later, a temperature of 103 F and vomiting developed. She was treated with antibiotics, and her complaints resolved as they had previously. She had felt well since. At no time had she had abdominal pain. She had undergone cholecystectomy elsewhere in 1948, and her gallbladder was said to have contained a single stone. Prior to this she had had colic off and on for two years but no jaundice. Also elsewhere, in July, 1956, something described as a polyp had been removed from the common duct, but apparently no stones had been present at that time.

Physical examination revealed a temperature of 100.4 F. The patient became nauseated and vomited during the examination and complained of being chilly. She did not appear to be jaundiced.

The results of laboratory examination were as follows: urinalysis, negative; hemoglobin and cells in the blood, normal values; sedimentation rate, 72 mm. in 1 hour; direct-reacting serum bilirubin, 0.7 mg.; indirect-reacting bilirubin, 0.8 mg.; serum lipase, 0.1 cc. of 0.1 N base per cc. of serum, and serum amylase, 106 units; cephalin-cholesterol-flocculation and thymol turbidity tests, normal value; prothrombin time, 19 seconds, and cultures of blood, negative on three occasions.

Roentgenograms of the thorax and urinary tract revealed no abnormality. An initial intravenous cholangiographic examination was reported as giving indeterminate results. On repeated examination a filling defect in the lower end of the common duct consistent with choledocholithiasis was noted.

At operation, on Oct. 14, 1957, a stone was removed from the lower portion of the common duct. The postoperative course was without complication, and the patient's temperature remained normal.

Again the history of previous cholecystectomy and current slight increase of the direct-reacting serum bilirubin, together with our recent experience in Case 1, led to the suspicion of choledocholithiasis. The results of intravenous cholangiography confirmed this suspicion. The patient wrote on Jan. 27, 1958, that she had had no recurrence of chills, fever, or vomiting since her operation.

CASE 3.—A 58-year-old housewife came to the clinic on Dec. 16, 1957, because of intermittent fever of eight weeks' duration. She had been examined here repeatedly since 1941 because of multiple sclerosis. Eight weeks prior to the current admission she had received one injection of Asian influenza vaccine. Ten days later she suddenly experienced a temperature of 102 F (oral), with mild shaking chills and associated "heaviness in the head." The fever lasted one hour and was followed by weakness and prostration, which disappeared after 48 hours. Similar attacks had occurred once weekly, for a total of eight; the last attack had occurred on Dec. 12. On one occasion her urine had been dark. Three days prior to admission she began to have pain in her left buttock; this had extended down the back of her left leg to the heel. Repeated examinations elsewhere had given negative results, and she had received no antibiotics. She had no gastrointestinal symptoms, specifically denying abdominal pain; at no time had she been jaundiced.

In 1954, cholecystectomy had been done because of typical biliary colic. At operation the gallbladder was described as being gangrenous; a large single stone was found therein; the common duct was not explored.

Physical examination revealed only findings relating to the multiple sclerosis and recent sciatica and consisting of right foot drop, hyperactive knee jerks, absence of right ankle jerk, positive Babinski sign on both sides, and positive Lasègue sign on the left.

The results of laboratory tests were as follows: urinalysis, Grade 2 albuminuria and Grade 3 microscopic hematuria; hemoglobin and cells in the blood, normal values; sedimentation rate, 54 mm. in 1 hour; urea, 22 mg. per 100 cc. of blood; direct-reacting serum bilirubin, negative, and indirect-reacting bilirubin, 0.8 mg.; retention of sulfobromophthalein in the serum 1 hour after intra-

venous injection of 5 mg. of the dye per kilogram of body weight, 20%; serum proteins, 5.6 gm. per 100 cc. and albumin-globulin ratio, 3.9:1.7; serum alkaline phosphatase, 130 units per 100 cc.; serum glutamic-oxalacetic transaminase, 7.20μM. per hour per cc.; thymol turbidity test, 1 unit; cephalin-cholesterol-flocculation test, negative.

Roentgenograms of the thorax did not disclose any abnormality, but those of the lumbar portion of the spinal column revealed moderate narrowing of the lumbosacral interspace.

On Dec. 19, 1957, the liver was palpable 1 finger-breadth below the right costal margin, and it had a firm round edge. On Dec. 23, intravenous cholangiographic examination was attempted, but the common duct was only partially filled by dye, and it was impossible to exclude stones therein.

The patient was dismissed on Dec. 25, to return in one month for further evaluation. She returned on Jan. 11, 1958, complaining of general malaise and of a daily elevation of temperature to 100 F (oral), with an occasional chill. Her urine had been dark intermittently, and on one occasion she had observed a "putty-colored" stool. Other than an oral temperature of 101 F, the results of physical examination were unchanged. On Jan. 14, an exploratory laparotomy was carried out. The liver appeared grossly normal. The common duct was considerably dilated, and three large stones with several smaller ones were removed therefrom. Biopsy showed Grade 3 subacute pericholangitis with some bile stasis. There were no postoperative complications.

The fact that this patient had previously undergone cholecystectomy, retained sulfobromophthalein in her serum at the end of one hour, and had an elevated value for serum alkaline phosphatase suggested hepatobiliary disease. Lymphoblastoma was also considered in the differential diagnosis. The intravenous cholangiograms were not helpful. Surgical exploration was advised because of the recurrent fever and indeterminate findings. Correspondence in February, 1958, established that the patient had had no recurrence of fever or other manifestation of biliary disease since her operation.

CASE 4.—A 69-year-old farmer came to the clinic on Jan. 4, 1955, complaining of loss of appetite and episodes of chills, fever, and sweats. His present illness began in 1952, with recurrent diffuse abdominal distress, nausea, and vomiting. In 1953, the episodes were further characterized by chills, fever, and sweats. In the ensuing two years he had been hospitalized several times because of these paroxysms.

During the three weeks preceding admission to the clinic he had had several, usually nocturnal, episodes during which he had a temperature of 105 F. He had lost 30 lb. since his illness began. He denied any abdominal pain over the last two years and said that he had never been jaundiced.

Physical examination revealed a temperature of 98.2 F. There was some epigastric tenderness on deep pressure, and the liver was just palpable on deep inspiration.

Laboratory and x-ray data were as follows: urinalysis, negative; hemoglobin and cells in the blood, normal values; urea, 38 mg. per 100 cc. of blood; sedimentation rate, 84 mm. in 1 hour. The roentgenographic appearance of the thorax and the gastrointestinal and urinary tracts was normal. The results of cholecystographic examination were interpreted as being indicative of a nonfunctioning gallbladder.

At operation, on Jan. 13, 1955, the gallbladder was found to be thick-walled but no stones were palpated. There was marked subacute hepatitis, with redness and firmness of the liver. The common duct was not enlarged, but two stones of the soft type, 1 cm. in diameter, were found impacted in the ampulla. The surgeon commented that he was amazed that this patient did not have clinical jaundice, since the tightly impacted stones could be dislodged only with difficulty. Cholecystectomy was performed. Biopsy of the liver showed Grade 3 subacute and chronic pericholangitis, with early biliary cirrhosis.

The roentgenographic finding of a nonfunctioning gallbladder appeared to warrant surgical exploration. The patient wrote on Jan. 30, 1958, that he had had no recurrence of fever since his operation and that he considered himself to be in excellent health.

CASE 5.—A 56-year-old farmer, a known diabetic for four years, first came to the clinic on April 24, 1953, because of diffuse abdominal pain. In 1951, after injections of typhoid vaccine, abdominal pain and a temperature of 103 F had developed. Cholecystographic examination was interpreted as indicating a nonfunctioning gallbladder, and cholecystectomy was performed. The gallbladder contained thick bile and purulent material but no stones. The common duct was not explored.

The patient had felt well until March, 1952, when he began to have fever (101 F), sweating, vomiting, and diffuse abdominal pain, which persisted for two weeks. In April, he had had three brief but similar episodes and was hospitalized when a temperature of 103 F was noted. While hospitalized he had severe diffuse abdominal pain, with circulatory collapse. He recovered from this promptly and was dismissed from the hospital, but he con-

tinued to have mild attacks of diffuse abdominal pain. Since his present illness began he had lost 25 lb.

Physical examination gave essentially normal results.

The results of laboratory examination were as follows: urinalysis, negative; hemoglobin and cells in the blood, normal values; sedimentation rate, 7 mm. in 1 hour; direct-reacting bilirubin, 1.0 mg., and indirect-reacting serum bilirubin, 0.6 mg.; serum lipase, 0.1 unit; prothrombin time, 18 seconds; retention of sulfobromophthalein in the serum at the end of 1 hour after intravenous injection of 5 mg. of the dye per kilogram of body weight, none.

Roentgenograms of the thorax revealed a tiny nodular lesion underlying the fourth intercostal space on the left, which was thought to represent an old inflammatory process. Roentgenograms of the abdomen showed a small rounded area of calcification in the subhepatic region, consistent with the presence of a gallstone. Roentgenographic examination of the upper part of the gastrointestinal tract gave negative results except for a small diverticulum in the second portion of the duodenum.

At operation a remnant of the gallbladder and the cystic duct were removed. The common duct was approximately three times normal size, and a stone approximately 8 mm. in diameter was found in the ampulla. Convalescence was uneventful.

The history of previous cholecystectomy, roentgenographic evidence of an area of calcification in the subhepatic region, and current slight increase of the serum bilirubin led to the diagnosis of choledocholithiasis. In answer to a letter of inquiry, his family physician wrote on Feb. 12, 1958, that the patient had not had any fever associated with upper abdominal pain since his operation and that, as a matter of fact, he had had no biliary disturbance.

CASE 6.—A 55-year-old man was referred to the clinic on May 7, 1951, because of fever of unknown origin. In 1949, he had had recurrent attacks of fever, chills, and weakness that lasted 24 hours; these had occurred once or twice a week over a three-month period. He had then been free of symptoms until December, 1950, when the episodes began again and lasted until his admission to the clinic.

Typical episodes usually began at about 11 a. m. Shaking chills lasting approximately an hour were followed by a temperature ranging up to 104 F; each episode would terminate with profuse perspiration. There were no symptoms between episodes, and to his knowledge he had never been jaundiced. At no time had he had abdominal pain. The physical examination gave essentially negative results.

The results of laboratory examination were as follows: urinalysis, negative; hemoglobin and cells in the blood, normal values; sedimentation rate, 33 mm. in 1 hour; direct-reacting bilirubin, 0.5 mg.; indirect-reacting bilirubin, 0.7 mg., and Kline reaction for syphilis, negative.

Roentgenograms of the thorax, a cholecystogram, and an electrocardiogram did not reveal any abnormality.

Despite the normal cholecystogram, it was decided to explore the patient's biliary tract. At operation, on May 21, 1951, the liver and spleen appeared to be enlarged. The gallbladder was tense and edematous and was filled with stones. The common duct was not enlarged, but when it was opened bile gushed forth under great pressure. Several small stones were found impacted in the ampulla.

The slight increase of serum bilirubin, despite the normal cholecystographic findings, led to exploration of the patient's biliary tract. The patient wrote on Jan. 26, 1958, that he had had no recurrence of chills, fever, or sweating since his operation.

Comment

Classically, the fever that bears Charcot's name is intermittent; that is, variable periods of pyrexia are separated by intervals of normal temperature. Recurring attacks of chills and sweats may be associated with the fever. Also nausea and vomiting may occur. Unlike our patients the victim is usually jaundiced at the time of the paroxysm, and the degree of jaundice varies from a fleeting subicteric tinge of the skin to persistent discoloration, which may deepen after each paroxysm of fever. There may or may not be a history of biliary colic, but some type of abdominal distress is the rule. Prostration during the febrile episodes may be great. The liver may be enlarged and tender, and the color of his excreta may vary. Mild to marked leukocytosis may occur during the paroxysm.

The syndrome was described by Charcot,[1] in 1877, and subsequently emphasized by Osler[2]; it has since been referred to as "Charcot's intermittent hepatic fever." Osler[2] described eight patients who had Charcot's fever, six of whom were women.

Four of our six patients were men. Jaundice was present in all of Osler's patients; while he had not seen a nonicteric victim of the syndrome, he pointed out that Charcot had had such a patient. In none of our six patients was there clinically detectable jaundice. Osler pointed out that the fever was paroxysmal, that the onset was sudden, and that the syndrome rarely persisted for an entire day. He had observed daily recurrences of fever as well as irregular intervals of freedom from it. He had also observed that severe rigors accompanied the fever in some patients, but other patients had had only sensations of coldness. In Osler's experience, abdominal pain of some sort was present as a rule. Four of our six patients had not had abdominal pain. The relatively good health of most victims of Charcot's fever in the intervals between the febrile episodes was also emphasized by Osler.

The syndrome is usually associated with a calculus in the common bile duct, and the intermittency of its manifestations is considered to reflect a ball-valve action of the stone.

The mechanism of Charcot's fever appears to be infectious and apparently reflects cholangitis associated with intermittent obstruction of the common duct. Such cholangitis may involve the intrahepatic biliary radicles and the parenchyma of the liver in addition to the extrahepatic bile ducts. Members of our group[3] have recently referred to the bacterial organisms responsible for cholangitis.

Chills and fever are absent in about two-thirds of the cases of choledocholithiasis. Even when these signs are present they rarely occur alone but are practically always a counterpart of jaundice and attacks of biliary colic. In patients with choledocholithiasis, abdominal pain is absent in about 20% and jaundice is absent in about 25%.

Our six cases of recurrent pyrexia indicate the need for investigation of the biliary tract in instances of fever of obscure origin. In patients who have been subjected to cholecystectomy previously, intravenous cholangiographic examination may be helpful. In some patients, laparotomy may be necessary to establish the diagnosis. In none of our six patients was there clinically detectable jaundice, but in four there were slight deviations from normal of the direct-reacting serum bilirubin, which added to the suspicion of obstruction in the common duct. Since Charcot's fever in these instances reflects a correctable lesion, the lesion should be diligently sought.

Summary

The differential diagnosis of recurring attacks of fever includes the intermittent fever associated with obstruction of the common bile duct. Charcot's fever without jaundice or pain characteristic of biliary colic might constitute an enigma. Reports on six patients whose fevers were associated with choledocholithiasis without jaundice are presented. In four of the six patients slight elevation of the values for direct-reacting serum bilirubin, in the absence of clinically detectable jaundice, was helpful in establishing the diagnosis. Four of these six patients had no abdominal pain. In patients who have fever that is not explained otherwise, roentgenologic investigation of the biliary tract should be carried out. Surgical exploration may be the only method of confirming or denying the possibility of Charcot's fever in some patients. A history of previous cholecystectomy in a patient with intermittent pyrexia demands careful exclusion of Charcot's fever.

Mayo Clinic.

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Bone Changes in Neurofibromatosis

Report of a Case with Coincidental Osteitis Deformans and Review of the Literature

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Introduction

Even before von Recklinghausen's original monograph, in 1882,[1] the literature has contained references to various bone changes complicating neurofibromatosis, e. g., bowing and pseudarthroses,[2] disorders of growth.[3] Indeed, Wilson[4] includes bone affection in his definition of the syndrome, and Saville et al.[5] state that neurofibromatosis is characterized by lesions of skin, nerve, and bone.

Diverse secondary features other than bony which are said to occur can be grouped into psychological and endocrine. Regarding the former, perhaps the most pertinent comment is made by Wilson,[4] "that some sufferers from a disease marked by unsightly deformities and disfigurements, especially when the face is concerned, should become sensitive, despondent or misanthropic need occasion no surprise." Authors further reflect that of diverse psychical disorders reported in connection with the malady none is specific and most are purely incidental.

Various investigators, including Preiser and Davenport[6] and Yakovlev and Guthrie,[7] have reported an increased incidence of mental backwardness in patients with neurofibromatosis. The evidence for this is not decisive, and it remains a widely held clinical impression that there is a preponderance of low-normal intelligence and lower intellectual grades in these cases.

Leader and Grand[8] believe that psychic disturbances are a result of endocrine influence.

A wide variety of endocrinopathies have been described as complicating neurofibromatosis. These include menstrual abnormalities, incomplete and delayed sexual development, acromegaly, cretinism, myxedema, tetany, and Addison's disease,[9] to which have been added hypopituitarism, dystrophia adiposogenitalis, and several polyglandular diseases.[10] Chromaffin tumors have been described,[11] as has precocious puberty.[12]

Gordon[13] wrote that nothing has been advanced to prove that the endocrine glands act in themselves as an etiological agent and that at most a common genetic factor may be assumed responsible for both sets of symptoms. Little has been reported from the morbid anatomical aspect of direct tumor involvement of endocrine glands.

Malignant change in a neurofibroma is in a different category from the foregoing. Hosoi, who made a special study of malignant change in neurofibromata, stated that mere extirpation of a malignant or even a benign tumor appears to stimulate another neurofibroma distantly located to sarcomatous transformation.[14] Hosoi also stated that malignant transformation takes place in about 13% of *all* cases of neurofibromatosis, whereas Holt and Wright quote 5.5% of their cases.[15]

Uhlmann and Grossman rejected biopsy of a confluent rope-like nodular neurofibromatous mass in the leg of a child of 2 years because of the risk of inducing a malignant metaplasia. For the same reason they refused to consider epiphyseal arrest by open operation to check the accelerated disproportionate growth of the leg. They maintain that diagnosis can and should be made without biopsy.[16]

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My own opinion is that tumors should be excised only for relief of physiological embarrassment caused by pressure, or where a particularly large tumor is constantly liable to injury, as on the beard area in the male—and then only after serious reflection.

While malignant change in neurofibromata is an observed fact, no specific syndrome of either mental illness or endocrine abnormality has been associated sufficiently often with neurofibromatosis to be considered a secondary feature.

Definition

Characteristically, von Recklinghausen's neurofibromatosis is a combination of neurofibromata and cutaneous café au lait colored patches and spots. Neurofibromata may be attached to the terminal twigs of peripheral nerves in the skin or to the cranial, spinal, and peripheral nerves.

The cutaneous tumors may be small (diameter a few millimeters), large (diameter a few centimeters), or massive (pachydermatocele, plexiform neuroma, elephantiasis neuromatosa), the latter group often being associated with abnormalities of growth.[17]

Their consistency may be hard or soft; they may be deeply set, sessile, or pedunculated and are painless on pressure. Usually stationary and quiescent for long periods, they may undergo active and extensive enlargement and new-crop formation, especially at stressful times, e. g., puberty, pregnancy, menopause, and illness.

Tumor regression is stated to be very rare.[16] Holt and Wright describe two instances.[15] In the first, a baby, considerable regression of cutaneous nodules associated with complete disappearance of multiple cystic bone lesions occurred. In a second baby, followed to its eighth month, they describe similar regression of cutaneous and osseous lesions.

A forme fruste is described and consists of the pigmented patches alone.[18-20] Secondary bone features may be present or develop, confirming the diagnosis. Thannhauser comments that café au lait spots are as much an indication for the diagnosis of neurofibromatosis as the cutaneous neurofibromatous nodule itself. He suggests that one should search for hidden involvement of other organs, especially the bones. Nodules almost invariably develop in later years.[12]

Heredity

Although a heredofamilial incidence was previously suggested,[21] it was not until 1918 that Preiser and Davenport reported an incidence of 43.5% in 115 offspring of patients.[6] They considered that the gene, a dominant, was transmitted equally by both sexes. They found that the disease tends to occur without a break in several generations, with a definite familial resemblance in the type and location of the principal tumors, the tendency to produce similar pigmentation, the tendency to confluent tumors (elephantiasis), and the tendency to sarcomatous change.

Opinions were succinctly summarized long ago by Feindel, quoted in 1909 by Harbitz, "Generalized neurofibromatosis is always congenital, often hereditary and sometimes familial."[22] But there are also cases in which there is no apparent familial or hereditary history.

Pathology

The nature and terminology of the swellings, which are so characteristic of this disease, remain in dispute. These swellings are "tumors" in the wide connotation of the word, but the problem of their hyperplastic or neoplastic nature has not yet been settled.[4]

Virchow, in the middle of the last century, called them false neuromas because of the striking overgrowth of the mesodermal connective tissue lining the nerve.[1,23,24] However, the presence of tissue with palisading nuclei and parallel fibers led Verocay to assume that the neoplastic cells were ectodermal sheath of Schwann cells and that the fibers were nerve fibers.[25]

Penfield and Young believed that the tumors were invariably made up of tissue

of tangled and reticular structure and sometimes areas of true perineural fibroblastoma,[26] while Wilson mentions that a few nerve fibers (with or without myelin sheaths) wind singly or in sparse bundles through the tumor, others keeping to the capsule.[4]

Bone Changes

In 1901, Adrian published a monograph on all the cases of neurofibromatosis reported up to that time and remarked on the frequent occurrence of changes in the bones.[27] Stahnke, in 1922, was the first to postulate that this was a systemic disease, basing his idea mainly on the changes in bones.[28]

As pointed out by Nørgaard[29] and by Thannhauser,[12] when the classical manifestations are absent, or only slightly developed, the diagnosis can be difficult, and in such cases radiological demonstration of the characteristic osseous changes may be of importance. Holt and Wright are more cautious, saying that none of the bone changes associated with von Recklinghausen's disease can be considered pathognomonic but they are frequently strongly suggestive of this condition.[15]

It was not until 1924 that the first attempt was made, by Brooks and Lehman, to classify and define these bone changes.[17] They described the following changes:

(1) Scoliosis.
(2) Abnormalities of growth of individual bones, most commonly associated with elephantiasic form.
(3) Irregularity of outline of bones, ranging from central and subperiosteal cysts to pedunculated subperiosteal tumors.

Subsequently different classifications were made by Moore[30] and by McCarroll,[31] but I have followed the classification of Holt and Wright,[15] which uses six headings, and have incorporated Swann's[32] addition, as follows:

(1) Erosive defects.
(2) Scoliosis.
(3) Disorders of growth.
(4) Bowing and pseudarthrosis.
(5) Intraosseous cystic lesions.
(6) Congenital anomalies.
(7) Osteomalacia (Swann).

(1) *Erosive Defects.*—Defects in the outline of the bones due to pressure from adjacent neurofibromata have been independently described and named by various authors as follows: erosive defects,[15] pressure defects,[28] outline irregularities (which term included irregularities arising from intraosseous tumors),[17] and pits and caves.[29]

Holt and Wright were the first to draw attention to the fact that neurofibromata of intercostal nerves produce the radiological picture of rib notching, previously considered pathognomonic of the intercostal arterial aneurysms occurring in aortic coarctation.[15]

Camp describes the radiological appearances of intraspinal neurofibromata, which over a three-year period at the Mayo Clinic constituted 23% of all spinal cord tumors operated upon, and in 42% of these the site was localized accurately by bone changes on the x-ray. These are erosive defects, affecting first the medial border of the vertebral pedicle, then the lamina, and then the posterior aspect of the body. He stresses that the first two stages are visible long before erosion of the body, which has a late radiological appearance.[33]

(2) *Scoliosis.*—Although not characteristic of this disease, scoliosis is almost universally present.[17] Miller[34] found it to be present in 43% of his cases with skeletal involvement, and it is certainly the commonest of the bony secondary features of this disease.

It has some predilection for the lower thoracic vertebrae but can occur at any level and is not infrequently combined with kyphosis, which on rare occasions is sufficiently acute to cause paraplegia.

Early reference to scoliosis in von Recklinghausen's neurofibromatosis was made by Adrian,[27] Preiser and Davenport,[6] Gould,[35] Weiss,[36] and Brooks and Lehman.[17]

How it occurs is not known. Gould suggested osteomalacic bone softening.[35] Brooks and Lehman suggested in some cases a local periosteal neurofibromatosis of vertebrae, in other cases limb inequalities, and in other cases developmental spinal abnor-

malities—or combination of these.[17] Further suggestions were put forward by Weber, namely, neurofibroma of spinal nerve,[37] and by Robb-Smith and Pennybacker, namely, neurofibromatous proliferation in the marrow spaces themselves.[38]

As Holt and Wright and also Swann do not include vertebral wedging in their classification of the bony abnormalities, this would seem to be an appropriate place to refer to it. Again, no satisfactory explanation has been established in spite of its frequent occurrence, and in one case which was examined after death, by Inglis, no recognizable neurofibromatous tissue was found in any one of the sections of the deformed vertebrae.[39]

(3) *Disorders of Growth.*—These are usually increased bone length and are associated with confluent rope-like neurofibromatous masses, giving rise to a picture of elephantiasis. Occasionally there is shortening instead of lengthening of bone.

As early as 1873, there was a report of hypertrophied phalanges in two siblings who were suffering from a "peculiar form of molluscum."[3]

The explanation of bone lengthening by Brooks and Lehman is one of increased vascularity produced by neurofibromatous tissue.[17] Nørgaard[29] used the phrase "embryonal defect."

Moore maintained that there exists a segmental relationship between the affected nerve and the bone. He considered that either directly or indirectly changes in the nerve were responsible for the "uncontrolled growth," which term embraced "hypertrophy" (overdevelopment), "hypotrophy" (underdevelopment), "distortion of growth" (scoliosis), and "change in the constitution of bone" (failure to unite after fracture). He found endarteritis in the bone arteries and suggested that endarteritis might account for mental and endocrine changes if it were generalized or widespread.[30]

(4) *Bowing and Pseudarthrosis.*—Bowing of a bone has been reported in association with neurofibromatosis, as has pseudarthrosis (failure to unite and formation of a false joint), either after a fracture or present at birth. It has been noticed that pseudarthrosis is more likely to occur in bowed bones in this disease. This was recorded as long ago as 1872, by Fremmert[2] and subsequently by Adrian[27] and by Ducroquet, who is widely quoted.[40]

Barber, who claimed to be the first to mention the association between pseudarthrosis and neurofibromatosis in the American and British literature, remarked that both ends of the pseudarthrosis develop normally. Of his five cases, pseudarthrosis followed fracture in one, osteoclasis in another, and osteotomy in a third. A fourth was seen, having had four operations for nonunion of a fracture in 10 months. After sequestrectomy, healing took place over many months. His fifth case was a 2-month-old girl with anterolateral bowing of the lower third of her right leg, which had been present since birth, in association with café au lait pigment of the skin (her mother had visible neurofibromata). In view of the uniformly bad result of interference during the growing years, her parents were strongly advised to have nothing attempted in the way of corrective surgery until after puberty.[41]

(5) *Intraosseous Cystic Lesions.*—These were first described by Brooks and Lehman and are rare. They considered that these lesions could be explained on the basis of periosteal nerve neurofibromata invading the bone, with bone-forming periosteum remaining on the outside. Thus cysts could be in the cancellous bone, cortical bone, or the subperiosteum or pedunculated from the bone. They stated that microscopical examination of one of these tumors showed that the central portion was composed of tissue similar to that found in the skin tumors, together with newly formed bone trabeculae.[17] Thannhauser believed that these bone cysts are fibromata with cystic degeneration and tried to establish the thesis that fibrous dysplasia of bone, or, as he called it, "osteitis fibrosa cystica localisata et disseminata," is not an independent

entity but can be related by its clinical and histological features to Recklinghausen's neurofibromatosis.[12] His arguments are refuted by Jaffe.[42]

(6) *Congenital Anomalies.*—A variety of congenital bony anomalies have been described in cases of neurofibromatosis, including spina bifida, cerebral meningocele, defects in fingers and toes,[43] fusion of vertebral bodies, congenital dislocation of hip, and clubfoot,[15] but the association is probably coincidental.

On the other hand, cranial deficiencies have been recorded sufficiently frequently to suggest that it is more than a coincidence, rather more instances being of orbital defects.[15,43-46] Peyton and Simmons presented 5 cases of their own and 20 more from the literature. They pointed out that these cases (children, as they usually are) have a pulsating exophthalmos due to transmitted pulsation of the cerebrum and not to expansion of orbital contents as in arteriovenous fistula. They also commented that there is no associated bruit, as with fistula.[46]

But they were also recognized in the last century, viz., Thomson (1900), "Plexiform neurofibroma may lodge in grooves or in actual gaps in bone e. g. flat bones of skull or roof of the orbit." [21]

(7) *Osteomalacia.*—According to Hagelstam [47] osteomalacic bone softening occurring in neurofibromatosis was reported by Königsdorf, in 1889; by Du Mesnil, in 1891; by Hoisnard, in 1898, and by Kolepke and by Gabriel, in 1911.

Gould examined histologically portions of the skeleton of five cases of neurofibromatosis who died. One of these showed the typical changes of osteomalacia during life and at postmortem examination; in one other the bones at autopsy were decidedly soft, although there was no gross skeletal deformity. The remainder were apparently free from any softening at all. The microscopical changes agreed with this—one marked, one less marked, the remainder normal. Microscopically, the affected bone was decalcified, i. e., osteoid. No biochemical investigations were recorded in the paper.[35]

Until the publication of Gould's paper, in 1918, no great notice had been taken of softening of the bones in cases of neurofibromatosis. Gould's honest statement of his observed facts could not be ignored, even though they could not be explained for many years.

Further cases have been reported, each without metabolic investigation. Merklen and Israel [48] described a case of von Recklinghausen's disease with general rarefaction of bone and with Milkman's syndrome, which is now generally believed to be due invariably to osteomalacia. In one of Nørgaard's cases there was a pseudofracture through the left inferior pubic ramus and another through the superior pubic ramus,[29] again pointing to osteomalacia. Hernberg and Edgren describe a case of "Looser-Milkman's syndrome with neurofibromatosis Recklinghausen and general decalcification of skeleton." [49]

Since then knowledge of the pathogenesis of osteomalacia and rickets has advanced with increasingly efficient methods of biochemical investigation, and it is now clear that these cases are due to a hereditary abnormality of the renal tubule, preventing reabsorption of phosphate, even when the serum phosphate level is severely subnormal.

Dent has classified cases of bone disease due to renal tubular abnormality, and his paper should be consulted for details.[50] The essential abnormality in all of the types listed is an inability of the renal tubules to retain phosphates, which are excreted in the urine no matter how low the blood level descends (renal phosphate leak). He described two such cases in association with neurofibromatosis, and cases are continually being reported.

Double Recklinghausen.—Clark et al., present, with pre- and postoperative biochemical proof, a case of von Recklinghausen's neurofibromatosis in which a parathyroid adenoma (causing the other "Recklinghausen's disease") was bene-

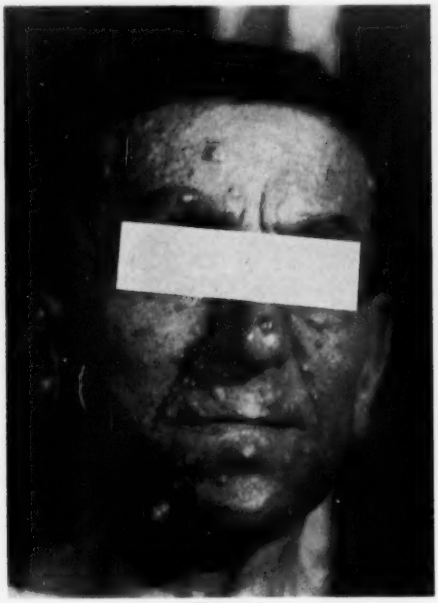

Figure 1

Fig. 1.—Facial neurofibromata.

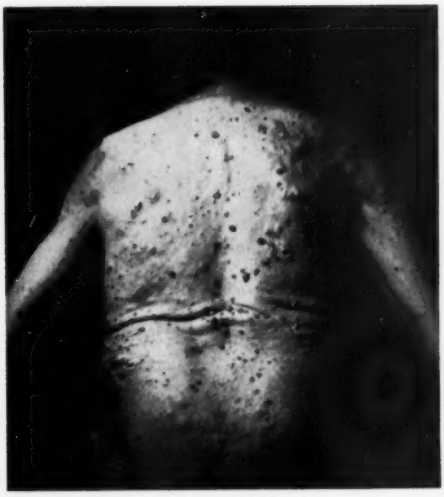

Figure 2

Fig. 2.—The back, showing neurofibromata and lumbar lordosis with transverse skin folding.

Fig. 3.—Café au lait patch.

Figure 3

Fig. 4.—Radiograph of right shoulder, showing cystic area in humerus.

Figure 4

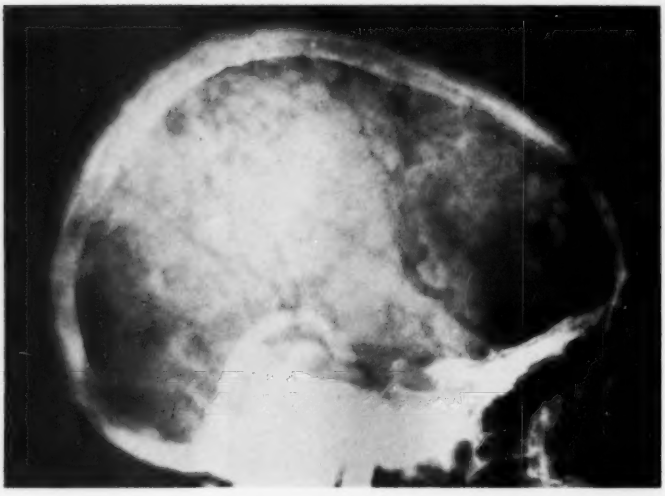

Fig. 5.—Skull radiograph, showing osteitis deformans.

ficially removed, even though it was further complicated by a liposarcoma.[51]

In reviewing the literature they found two previous claimants to the "double Recklinghausen," [52,53] but in neither case were both diseases proved present, and they therefore appear to be the first to have recorded this coincidence.

Fig. 6.—Radiograph of left hip, showing osteitis deformans of pelvis and femur and small femoral cyst.

Report of Case

A dock capstan man, aged 58, was referred to this unit in February, 1955, for investigation of a cyst in the right humerus (by Dr. I. C. Cowan, Consultant in Physical Medicine).

He complained that following a fall onto the right shoulder four months previously he experienced pain and stiffness in it on any movement. He had also been getting low back pain daily for five years and occasional pains in the right lower leg.

He was subject to winter cough, present currently over the previous three months and productive of yellow sputum but no hemoptysis.

There were multiple subcutaneous and cutaneous lumps, some hard, some soft, some large, some small, some deeply set, and some pedunculated (Figs. 1 and 2). They were prolific on the face and trunk, less numerous on the upper arms and thighs, fewer still on the forearms, and scanty below the knees. He gave their onset as during the 1914-1918 war (age 17-21), since when they have increased very slowly. Nevertheless, he gave a history of having had "a tumor under the right arm" removed when aged 10 years.

In addition, there were on the skin numerous café au lait patches (Fig. 3.) and multiple pinpoint freckles, thought to have been present since birth. The patient was not aware of any other family incidence of either pigmentation or lumps.

His sputum was purulent, and examination of the lungs revealed evidence of infection and some collapse at the left lung base. In view of the possibility that this may have been due to a mollusc in the bronchial tree he was bronchoscoped by Mr. S. G. Griffin, who reported green pus in the left stem and lower lobe bronchi. The mucosa bled on touching, but there was no evidence of neoplasm.

On admission his blood pressure was 240/140; this subsequently fell to 150/100, and there was nothing to suggest that the hypertension was malignant, nor was there any clinical evidence to point to a pheochromocytoma. ECG was normal.

Skeletal System.—Movement at the right shoulder was grossly limited in all directions by pain. There was slight upper thoracic scoliosis convex to the right and a marked degree of lumbar lordosis with transverse skin folding (Fig. 2.) unaffected by trunk flexion. In addition, the right tibia was slightly thicker than the left.

Radiological Appearances. — Right Shoulder: Some expansion and relative translucency of the upper metaphyseal end of the humerus (Fig. 4).

Spine: Collapse of the 8th and 11th thoracic vertebrae.

Skull, Pelvis, and Upper Femora: Osteitis deformans. There was a small cyst in the upper, medial part of the left femoral shaft (Figs. 5 and 6).

Long Bones: Apart from the cysts in the upper ends of the right humerus and the left femur and the gross Paget's changes of the upper femora, there was a general slight widening of the bones, more marked in the right tibia.

Chest: Much increased density in the left lower zone, with elevation of the left dome of the diaphragm. Slight cardiac displacement to the left. The lateral view showed the density to be lying posteriorly and was compatible with infection with collapse. The right dome of the diaphragm was rounded.

Other Investigations.—Hb.: 63%, with hypochromia, slight microcytosis, and polychromasia of the red cells. E. S. R.: 49 mm. in one hour. Wassermann and Kahn reactions: negative. Serum calcium: 10.0 to 10.8 mg. per 100 ml. Serum inorganic phosphorus: 4.2 to 4.4 mg. per 100 ml. Serum alkaline phosphatase: 38 to 50 K. A. units per 100 ml. Serum acid phosphatase: 1.3 K. A. units per 100 ml. Mid-stream urine specimen: normal. Blood urea: 30 mg. per 100 ml. Stool tests for occult blood: 2 positive, 1 negative.

Comment on Case

The inclusion of all the findings under one diagnostic heading proved impossible. The patient obviously was the subject of at least two diseases: neurofibromatosis and osteitis deformans.

The two collapsed vertebrae provoked a variety of suggestions centered around a possibility that they were the seat of malignant deposits. The primary malignancy was postulated variously in Pagety bone, in a neurofibroma, and in the lung.

The cyst in the humerus was similarly the subject of speculation, ranging from a simple "idiopathic" bone cyst to a malignant deposit.

At this stage, in the absence of any incontrovertible evidence of new growth, I took the view that the humeral cyst, the femoral cyst, the collapsed vertebrae, and the scoliosis were all (nonmalignant) osseous complications of neurofibromatosis. This grouped the diagnoses as follows: (1) von Recklinghausen's neurofibromatosis with three forms of bone complications, viz., scoliosis, vertebral collapse, and two bone cysts; (2) osteitis deformans; also (3) infection-collapse of left lung base, and (4) hypertension.

When his progress was followed four months after his discharge from the ward his general health was being poorly maintained, without any definite new development. The large neurofibroma on the right of his chin was removed under local anaesthesia, as a result of cumulative complaints from the patient that it made shaving both irksome and dangerous.

The patient was not seen again at the hospital, but recent communication with his practitioner elicited that he had gradually deteriorated and died at home eight months later. No autopsy was held, and death was certified from asthenia due to neurofibromatosis.

Associated Paget's Disease

I have been able to find two references to Paget's disease of the bones complicating neurofibromatosis.

The first is by Austregesilo and do Couto, in 1930, whose patient, a woman of 68, had the classical, visible, multiple tumors and café au lait skin pigmentation and certain

bone changes which the authors ascribed to a forme fruste or early degree of Paget's disease. They reported transverse flattening and anterior bowing of the left tibia and increased thickening of the bones, especially the clavicles. No biochemical details were mentioned.[54]

These authors undoubtedly had reservations about the diagnosis of osteitis deformans in their patient and reiterate that the condition *restait incomplète*. Wilson refers in his textbook to this case and comments that the Paget's disease ". . . seems to have been a hyperostosis due to periosteal tumour formation."[4]

Austregesilo and do Couto include photographs of the actual leg deformity and of its radiograph, and indeed this could be interpreted as the bowing which occurs (most commonly in tibiae) as one of the complications of neurofibromatosis described earlier.

The second reference[55] is that of Fairbank, in 1950, who states briefly, "neurofibromatosis, Paget's disease and sarcoma of the pelvis were associated in one case known to us, a man of fifty three years." My case would therefore appear to be the second to be reported and the first in which the Paget's disease was present together with neurofibromatous bony complications.

Paget's disease of the bones or osteitis deformans is known to be a common ailment affecting men and women over 40. Schmorl reports a 3% incidence from 4,614 necropsies.[56] Collins reports a 3.7% incidence from 650 necropsies.[57] Kellgren and Lawrence, quoted by Luxton,[58] from a radiological survey of 381 men and women aged from 55 to 64 found an over-all incidence of 2.4%.

That a patient with neurofibromatosis living into middle age may develop osteitis deformans should therefore occasion no surprise, and no definite connection between the two diseases need be assumed.

Summary

The occurrence and importance of bony changes as a secondary feature in von Recklinghausen's neurofibromatosis are emphasized, and the literature on this subject, reviewed.

A case of neurofibromatosis with scoliosis, vertebral collapse, and long bone cysts, complicated by coincidental osteitis deformans, is presented.

The late Dr. O. Olbrich gave permission to publish details of this patient; Dr. J. B. Holroyd furnished the radiological reports, and Mr. Norman Stainsby supplied the photographs.

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Carcinoma of the Thyroid at Autopsy

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A number of writers [2-4] have commented on the relatively low incidence of carcinoma of the thyroid in autopsy material in comparison with the frequency with which the diagnosis is made on thyroid glands which are surgically removed. It has been suggested that either the histologic diagnosis of carcinoma is incorrect in some of these cases or the histologic appearance is not matched by biologic aggressiveness. Such assumptions have naturally led to the viewpoint that certain therapeutic measures commonly employed in the treatment of malignant tumors are unnecessary.

The purpose of this report is to give the actual incidence of carcinoma of the thyroid in patients studied at autopsy in a general private hospital. The thyroid glands were routinely removed by residents; they were encouraged to take blocks of tissue from nodules and scars for microscopic examination.

The accompanying Table lists all of the 32 carcinomas of the thyroid encountered in the autopsy material at this institution during the years 1948 through 1955. Approximately 2,000 autopsies were performed during this period. Excluding lymphoma and leukemia, approximately one-fourth of the patients in this series died of carcinoma. Eleven of the deaths were due to carcinoma of the thyroid. Examination of 6 of the 21 other patients with histologically malignant neoplasms of the thyroid disclosed metastases. Metastasis certainly must be regarded as an indication of biologic aggressiveness. Two per cent of cancer deaths at this institution were therefore due to thyroid cancer; potentially fatal carcinoma of the thyroid was present in an additional one per cent.

At least 2 of the 11 thyroid carcinomas which killed were actually considered carcinomas of the lung; 3 others could also have been so misinterpreted. It therefore seems possible that in other institutions instances of actual thyroid carcinoma may be overlooked among the many carcinomas of the lung which are seen so commonly in all hospitals.

In three cases of the present series a 15- to 18-year period elapsed between the original thyroidectomy and the appearance of clinically significant metastases. Conversion from a presumably low-grade papillary growth to a highly malignant pleomorphic and giant-cell variety took place more than once and indicates that an arbitrary separation into relatively low-grade and relatively high-grade cancers may be unrealistic.[5] The need for prolonged follow-up has become increasingly evident in a number of common tumors. Five-year follow-up now means little, and even a ten-year follow-up is beginning to lose some of its significance. A comparable malignant tumor which gives the appearance of benignity and which runs as prolonged a course as that of the papillary tumors of the thyroid [6] is the carcinoid of the intestine or lung.

We agree that for purposes of diagnosis and therapy so-called lateral aberrant tumors should be regarded as metastases, and we must concede that a tiny tumor of the thyroid can be missed. Furthermore, since certain papillary tumors of the thyroid have the same tendency to sclerosis and regression which characterizes the chorioepithelioma of the testis and the duct carcinoma of the breast associated with Paget's disease, a

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Characteristics of Thirty-Two Cases of Carcinoma of Thyroid

Patient No.	Sex	Age	Clinicopathologic Data	Lesions of Thyroid
			Group I, Occult Carcinoma	
1	F	65	Carcinoma of pancreas	Focus of papillary carcinoma; thyroid weight, 15 gm.
2	M	40	Rheumatic heart disease	Thyroid weight, 20 gm.; microscopic fibrotic focus containing neoplastic acini
3	M	46	Syphilitic aortitis	Thyroid weight, 33 gm.; 0.5 cm. nodule of papillary carcinoma
4	M	63	Diabetes mellitus Mesenteric thrombosis	Thyroid weight, 22 gm.; 0.5 cm. nodule of papillary carcinoma
5	F	54	Carcinoma of bile ducts	Thyroid weight, 12 gm.; 0.5 cm. nodule of papillary carcinoma
6	M	58	Myocardial infarction	Thyroid weight, 25 gm.; 2 nodules in lower pole (larger, 0.5 cm.) of papillary carcinoma
7	M	68	Carcinoma of stomach I^{131}-induced myxedema	Thyroid weight, 6 gm.; 0.5 cm. focus or papillary carcinoma
8	F	55	Carcinoma of colon	Thyroid weight, 20 gm.; papillary carcinoma in small fibrotic nodule
9	F	62	Cirrhosis of liver	Thyroid weight, 15 gm.; 0.4 cm. nodule of papillary carcinoma
10	M	62	Hypertension & asthma	Thyroid nodular; weight, 41.5 gm.; small focus of focally calcified papillary carcinoma
11	M	68	Pneumonectomy for carcinoma Occult carcinoma, prostate	Thyroid weight, 55 gm.; many colloid nodules & 1 focus of papillary carcinoma
12	M	94	Myocardial infarction	Thyroid weight, 18 gm.; 0.8 cm. calcified & ossified papillary carcinoma
13	F	70	Mastectomy for carcinoma Fracture of femur & osteomyelitis	Thyroid nodular; weight, 25 gm.; 1 focus of papillary carcinoma
14	F	72	Gastrointestinal hemorrhage Occult carcinoma of lung	Small thyroid with sclerosing follicular carcinoma
15	F	79	Myocardial infarct	Thyroid weight, 5.5 gm.; 2 0.3 cm. calcified nodules, 1 an adenocarcinoma
			Group II, Metastasizing Carcinoma, Nonfatal	
16	M	66	Mitral stenosis	Metastatic papillary carcinoma of thyroid type in cervical lymph node & lung; thyroid weight, 25 gm.; primary not found
17	F	36	Mitral stenosis	Metastases of differentiated follicular carcinoma of thyroid type in 2 cervical lymph nodes; thyroid weight, 13 gm.; primary not found
18	M	49	Cerebral hemorrhage	Thyroid weight, 23 gm.; several foci of papillary carcinoma & cervical lymph node metastasis
19	M	83	Carcinoma of prostate Septicemic pneumonia	Thyroid weight, 32 gm.; multiple colloid nodules, focal calcification & papillary adenocarcinoma with metastasis in cervical lymph node
20	M	34	Tetralogy of Fallot	Metastatic papillary adenocarcinoma of thyroid type in a cervical lymph node; thyroid weight, 18 gm.; primary not found
21	M	74	Stokes-Adams syndrome	Thyroid weight, 13.5 gm.; partially calcified 0.8 cm. nodule microscopically sclerosing adenocarcinoma; pulmonary metastasis
			Group III, Fatal Carcinoma	
22	M	72	Rapidly developing mass in neck; death in 2 mo.	320 gm. soft pale tumor mass replacing thyroid & extending into mediastinum; spindle-cell carcinoma
23	M	56	Surgical resection of papillary carcinoma, 1949; treated with I^{131}; died 1953	Radioiodine atrophy of thyroid; metastases to lymph nodes & bone with pattern of mature thyroid tissue
24	M	52	Thyroid lobectomy & radical neck dissection for undifferentiated carcinoma in 1952; external irradiation, radioactive chromic phosphate into pituitary; died February, 1955	Thyroid weight, 11.5 gm.: residual nodule of papillary carcinoma; widespread metastases, undifferentiated, with foci of suggestive papillation
25	F	55	Right lobectomy for spindle-cell carcinoma of thyroid; postoperative death	Residual 0.6 cm. nodule of anaplastic spindle-cell carcinoma: widespread metastases, including heart & aorta with carcinomatous valvulitis & coronary embolism
26	F	70	Node in posterior triangle of neck for "years"; respiratory infection; pulmonary metastases (x-ray)	Thyroid weight, 317 gm.; substernal extension: metastases & primary tumor of spindle-cell type

Patient No.	Sex	Age	Clinicopathologic Data	Lesions of Thyroid
27	F	40	Radioiodine therapy for hyperthyroidism & goiter; thyroidectomy revealed solid & follicular carcinoma in 1952; local recurrence, radioiodine therapy, pulmonary metastases, external irradiation; death 1955	Cicatricial fibrosis in bed of thyroid; regional & widespread metastases; microscopically sarcomatoid, follicular & occasional papillary patterns
28	F	42	Thyroidectomy 1930; chest pain, cough, fever, bronchial biopsy 1948 with diagnosis of epidermoid carcinoma; death 18 yr. after thyroidectomy	Residual thyroid not remarkable; pulmonary metastases consistent with carcinoma of lung but foci of papillary & follicular tumor found
29	M	73	Papillary carcinoma of thyroid removed, 1933; irradiation for recurrence, 1936; dysphagia & death, 1948	10 cm. mass fixed to trachea replacing thyroid; pulmonary metastases of giant-cell type with papillary & follicular components
30	F	75	Papillary carcinoma of thyroid removed, 1933; 1948, recurrent tumor compressing trachea; death	5 cm. mass posterior to right sternocleidomastoid muscle; 3 cm. mass on left side of trachea; regional & pulmonary metastases of giant-cell type
31	F	47	Diffuse tumor seen on x-ray; adenomatosis or alveolar adenocarcinoma of lung versus metastatic tumor	Pulmonary metastases simulated alveolar adenocarcinoma of lung, but 29 gm. thyroid contained small focus of papillary adenocarcinoma recognized only after microstep sections
32	F	39	1952, total thyroidectomy for carcinoma; lymph node contained tumor that was papillary, follicular, & undifferentiated; June, 1954, metastases to lung, skull with no I^{131} pickup; July 1954, radioactive chromic phosphate injected into pituitary followed in 1 mo. by diabetes insipidus; Oct., 1954, cough, shortness of breath, blurred vision, hoarseness; deep x-ray to pituitary & radio cobalt therapy to pulmonary metastases; death, Dec., 1954	Metastases of undifferentiated type widespread, including heart & brain; pituitary: partial destruction of posterior lobe by chromic phosphate; extensive pulmonary metastasis

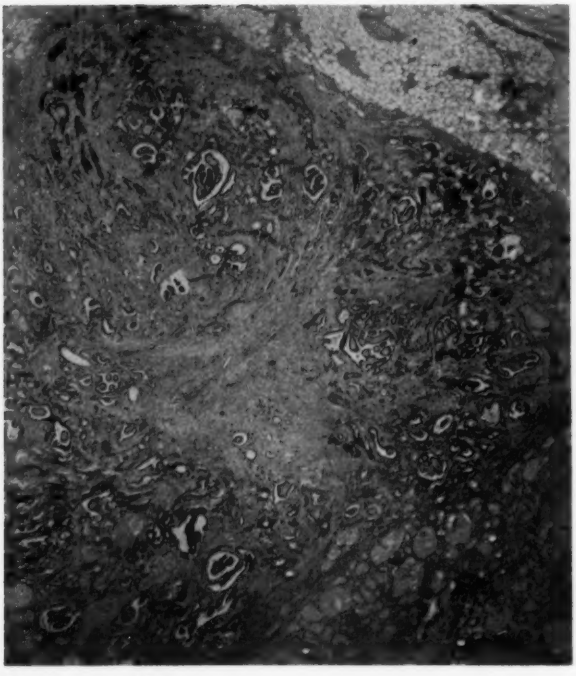


Fig. 1.—Low-power view of an occult papillary adenocarcinoma of the thyroid (Case 4). This particular one is an example of the so-called sclerosing nonencapsulated variety.[10] No metastases found; × 15.

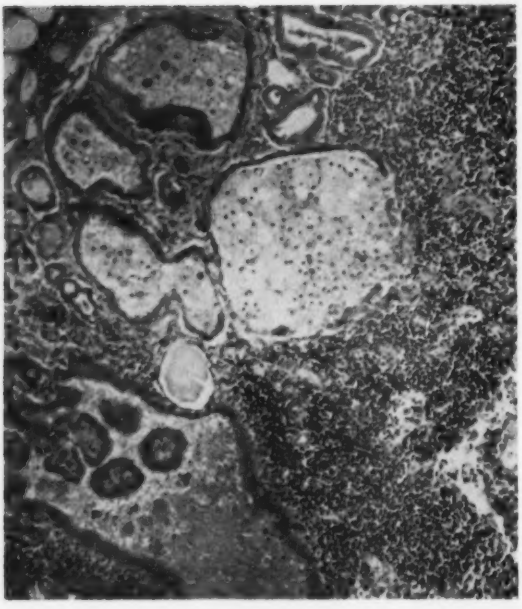


Fig. 2.—Metastasis in a cervical lymph node from an occult papillary adenocarcinoma of the thyroid gland (Case 19). There were no distant metastases; × 100.

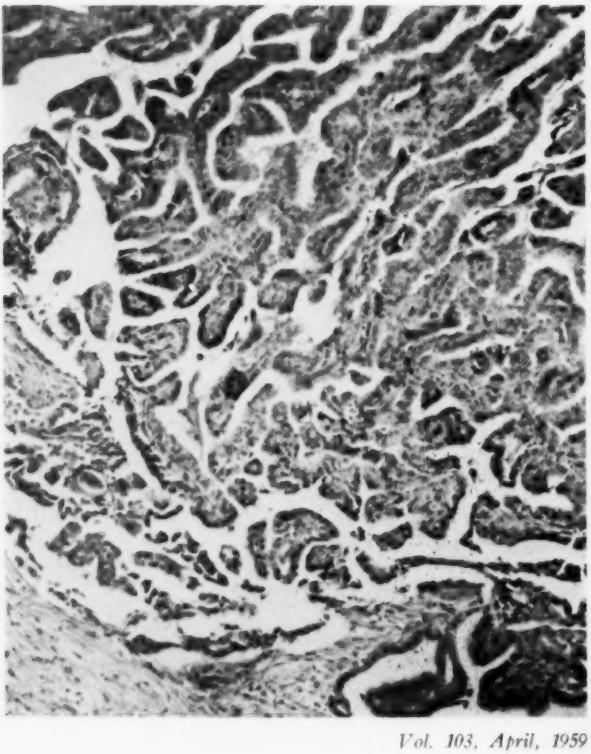


Fig. 3.—Papillary adenocarcinoma removed in 1933 (Case 30). Same patient as in Figure 4; × 100.

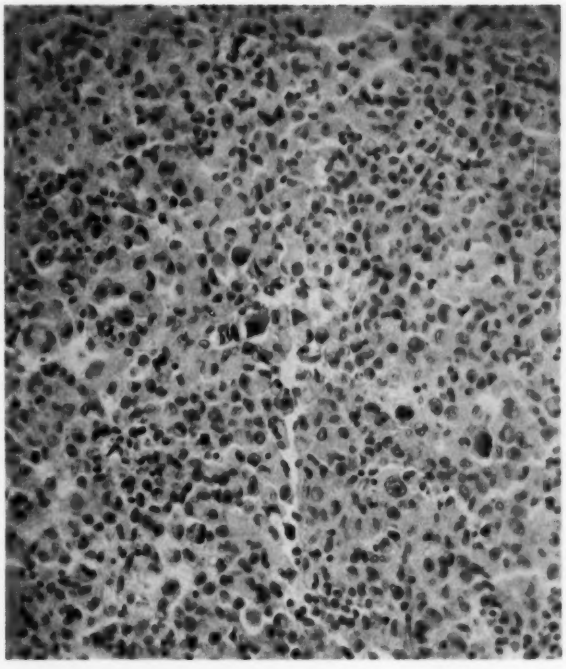


Fig. 4.—Same patient as in Figure 3 (Case 30). Shows undifferentiated pulmonary metastases 15 years after removal of papillary thyroid tumor in Figure 3; × 180.

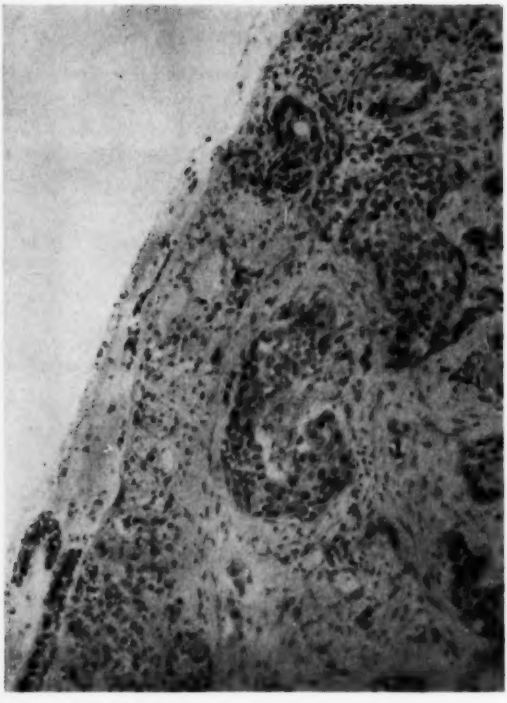


Fig. 5.—Biopsy specimen of a bronchus diagnosed as epidermoid carcinoma in a patient (Case 28) who died 18 years after thyroidectomy. The patient was considered to have carcinoma of the lung until microscopic study of the pulmonary tumor revealed the frank characteristics of thyroid carcinoma (Fig. 6); × 110.

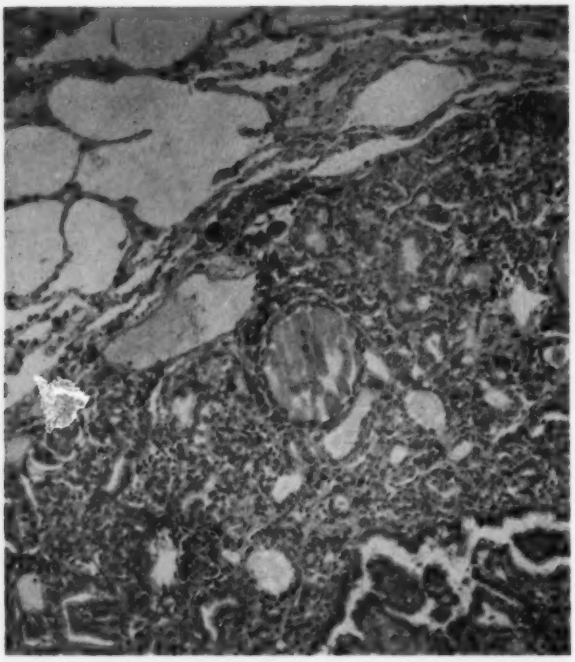


Fig. 6.—Same patient as in Figure 5. Papillary and follicular features in pulmonary tumor (Case 28), which indicate metastases from thyroid carcinoma rather than primary carcinoma of the lung; × 100.

cicatrix must be sought in the gland if a tumor is not found. However, in some of our cases neither a primary tumor nor a cicatrix was found despite step sections of the thyroid gland.

Comparisons between the incidence of malignant tumors in a given organ of autopsied patients and in surgical specimens of the same organ may be misleading. When the numbers of diagnoses made during the same period in our departments of surgical pathology and pathologic anatomy were compared it was found that carcinomas of the kidney, colon, and even breast came to autopsy as infrequently in comparison with the number of times the diagnosis was made on surgical specimens as did carcinoma of the thyroid. Three other common tumors were selected for specific comparison. The ratio between surgical pathologic and anatomic diagnoses of carcinoma of the thyroid was 8:1; in carcinoma of the uterus

Fig. 7.—Radiologic appearance of a pulmonary metastasis from carcinoma of the thyroid, which simulates the radiologic appearance of carcinoma of the lung. Same patient as in Figure 8.

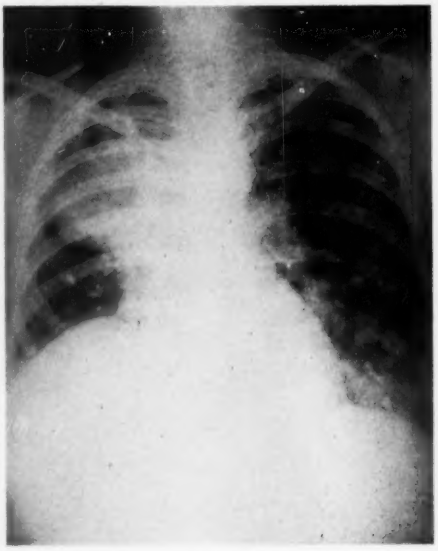


Figure 8

Fig. 8.—Gross appearance of lung from same patient as in radiograph in Figure 7. Relation to bronchus and general appearance of this metastasis shows how thyroid carcinoma can simulate the appearance of carcinoma of the lung.

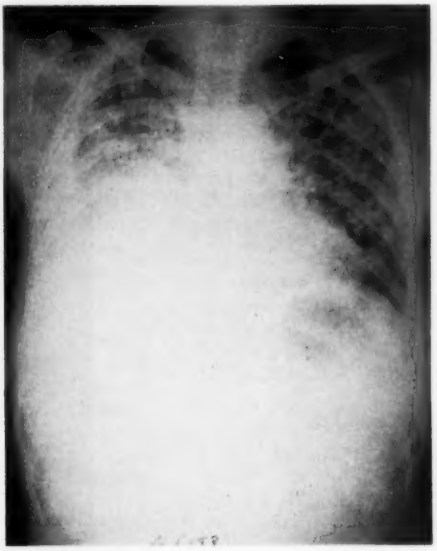
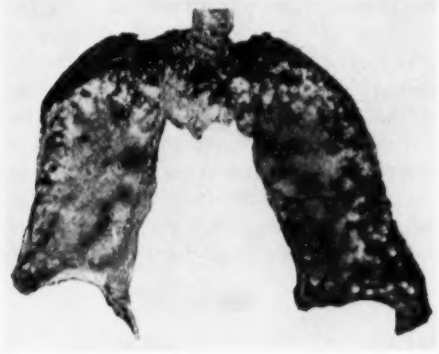


Figure 9

Fig. 9.—Radiologic appearance of chest film from patient in Case 31. Same patient as in Figures 10 and 11. Clinical diagnosis lay between pulmonary adenomatosis and metastatic carcinoma.

it was 6:1. The stomach and the lung gave ratios of 3:1 and 2:1. Such comparisons should not be taken to indicate more than that certain carcinomas appear with relatively greater frequency among those patients who enter operating rooms than they do among those who are taken to autopsy laboratories.[7-9] These two groups are skewed samples of the general population, and several successive selective samplings have obviously been made before the final composition of the two groups is determined. The implicit assumption that they are comparable samples of the general population is obviously in error.

Fig. 10.—Gross appearance of lungs from same patient (Case 31) as in Figures 9 and 11. Note how pattern of carcinomatous pneumonia simulates alveolar adenocarcinoma or adenomatosis. This patient was not diagnosed as carcinoma of the thyroid until after the autopsy.



Another set of comparisons may be relevant. Through the courtesy of Dr. Lester Breslow, of the California State Department of Health, figures were made available on the number of cases of carcinoma of the thyroid, uterus, stomach, and lung which had been recorded in the California State Tumor Registry. The ratio of registered cases to Registry deaths during a given period was as follows: thyroid, 3.4:1; uterus, 2.4:1; stomach, 1.3:1; lung, 1.4:1.

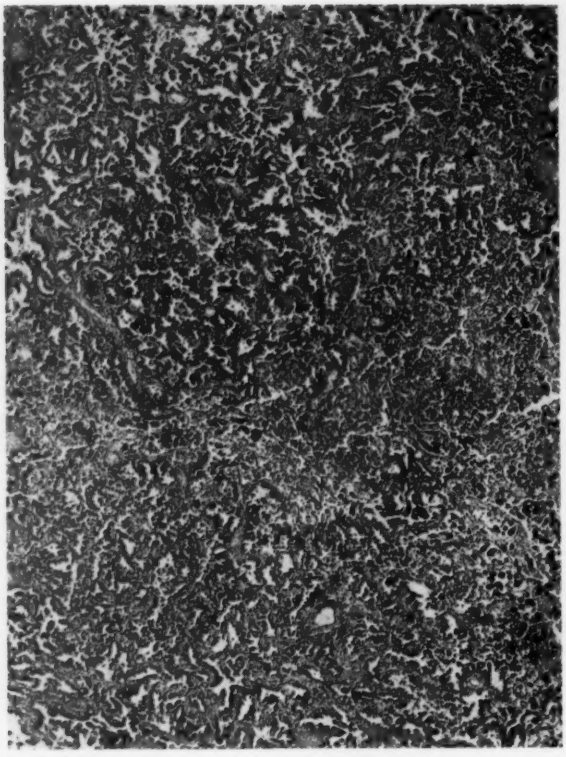


Fig. 11.—Microscopic appearance of pulmonary metastasis from unsuspected thyroid carcinoma, simulating alveolar adenocarcinoma of the lung. Same patient as in Figures 9 and 10 (Case 31); × 38.

Fig. 12.—Cardiac valvular and aortic metastases of thyroid carcinoma. The thickening and distortion of the valve cusps and the plaque-like thickening of the aorta were both due to tumor. There was also a coronary tumor embolus, which was responsible for death after resection of the thyroid tumor (Case 25). Cardiac metastases were present in three of the patients in this series.

Cases are usually registered at the time the diagnosis is first made, and hence surgical procedures are often involved. Therefore the high ratio for carcinoma of the thyroid or uterus and the low ratio for the tumors of the stomach or lung are reminiscent of the surgical-autopsy ratios presented earlier in the paper. The thyroid and uterus are more accessible to surgery than are the stomach or lung. Finally, the following information, which bears out such an interpretation, was also supplied by Dr. Breslow. Thirty per cent of all persons who died of cancer in California during the year 1950 had been previously registered in the California Tumor Registry. This percentage varied considerably for tumors of different organs. It was considerably lower for carcinoma of the lung (25%) and of the stomach (22%) than for carcinoma of the uterus (41%) or of the thyroid (58%).

Summary

Thirty-two instances of carcinoma of the thyroid were found in a series of approxi-

mately 2,000 autopsies. Eleven of the thirty-two tumors were responsible for the patient's death, and in six others there were microscopic metastases from an otherwise presumably occult carcinoma. In some cases there was a long interval between the discovery of the primary growth and the development of the fatal metastases—18 years in one patient. Primary tumors which were papillary at their inception sometimes converted in whole or in part to pleomorphic varieties in their subsequent metastases. Several of the metastasizing tumors simulated carcinoma of the lung, and some were so diagnosed. An apparent disproportion between the number of diagnoses of carcinoma of a given organ based on study of surgical specimens and the number disclosed by examination of autopsy material is probably due to factors other than the degree of malignancy of the tumor.

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Serologic Response to Far East Influenza

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In the spring and autumn of 1957, United States military personnel in the Far East were exposed to an influenza epidemic. Viral strains demonstrated an antigenic composition markedly different from those recovered in previous years.[1] In the course of testing several hundred sera for the development of antibody to influenza virus, excellent results were obtained with the complement-fixation (CF) test in contrast to the standard hemagglutination-inhibition (HI) test, which often failed to demonstrate a diagnostic rise in antibody titer in sera positive by CF. Studies were undertaken in the autumn and winter of 1957-1958 to investigate the CF- and HI-antibody response to influenza in young susceptible adults in the Far East.

Methods and Materials

Antigens and Tests.—Complement Fixation: Far East-virus Strain A/JAP/307-57 was inoculated into 10-day-old embryonated eggs, and the uncentrifuged allantoic fluid was used as antigen in the complement-fixation test as described by Lennette,[2] with the following modifications: Serial twofold dilutions of an initial serum dilution of 1:4 were incubated 18 hours at 4 C with 2 full units of guinea pig complement and 4 units of antigen. Three units of amboceptor were used in the hemolytic system. The tests were read after a final incubation for 30 minutes at 37 C.

Hemagglutination and Hemagglutination-Inhibition: Far East-virus Strain A/Formosa/313-57 was used in the HI test. This strain was relatively insensitive to nonspecific serum inhibitors.[3,4] The hemagglutination-inhibition test was done by the pattern method with use of human "O" RBC.[4] Sera were inactivated at 56 C for 30 minutes. Initial dilutions of sera were 1:4. All serum titers are expressed as reciprocals of the initial dilution prior to the addition of other reagents.

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Sera.—Specimens from two groups of patients were studied. 1. One consisted of 271 military personnel ill with influenza between April and August, 1957 (48 Army, Navy, and Air Force installations, Far East Command). Several strains of Far East virus were isolated from this group. 2. The other consisted of 23 young adults (ages 18-30) with clinically diagnosed influenza in the autumn of 1957 from whom three or more serum specimens were obtained. The patients in this group were bled at 0-1, 2-3, 6-7, 13-14, and 20-21 weeks after onset of disease. All had been immunized against Types A and A' influenza one to two years prior to their exposure to Far East influenza. None had any recurrence of influenzal symptoms or were vaccinated against influenza during the study period. It was not possible to obtain specimens from all 23 patients during the test period, owing to rotation of a few personnel. Seven strains of Far East-influenza virus were isolated from patients in this group.

Upon receipt, sera were transferred to screw-capped Lusteroid tubes and stored at —20 C. All sera from the same patient were tested simultaneously by HI and CF. The geometric mean titer (GMT) was calculated by the method of Kenney.[5] All sera with no demonstrable titer at 1:4 were arbitrarily assigned a titer of 1:2.

Results

Of 271 paired sera submitted for serologic confirmation of influenza, 204 demonstrated a fourfold or greater rise in CF antibody. Two paired sera had titers of 1:32; eight sera had titers of 1:16, and thirteen sera showed only a twofold rise. Of the 271 paired sera, 30 demonstrated titers of less than 1:16 with no antibody rise in the convalescent specimens. These 30 were also negative by HI. Fourteen sera were anticomplementary.

The Table illustrates the development of CF antibody in 145 patients for whom sufficient clinical data were submitted. Diagnostic antibody rises were seen in the 6- to 9-day period, with peak values 10-21 days

Serum Antibody Titer in Relation to Stage of Illness in Far East Influenza

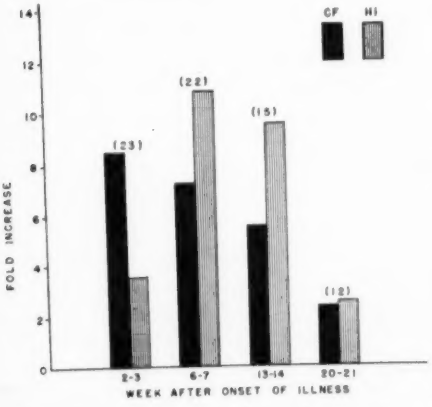
Group 1	Days	Titer <4	4	8	16	32	64	128	>256	Total	Geom. Mean Titer
CF test (145 positive paired sera)	0-2	31	32	18	3					84	3.5
	3-5	19	21	17	3					60	4.2
	6-9		1	2	2	5	2	1	1	14	28.8
	10-12				1	4	7	1	3	16	66.7
	13-21				9	25	24	22	11	91	64.4
	22-43				2	9	9	4	1	25	52.7
HI test (102 paired sera)	0-2	14	31	17	4	2				68	4.8
	3-5	3	16	9	4	1				33	5.7
	6-9		5	4						9	5.4
	10-12		3	3	6	1	1			14	10.7
	13-21	1	7	21	18	12	5			64	13.4
	22-40		1	3	8	2	2			16	16.7

after onset of disease. From this group 102 paired sera were also tested by HI (Table). Titers were low, and diagnosis could be established in only 44 patients.

In 23 patients (Group 2), CF antibody appeared at diagnostic levels by the third week, as had been seen in the larger group, of 145 patients. However, HI antibody did not attain diagnostic levels until after the third week. This is plotted, in terms of fold increase of antibody, in the Chart. The GMT's of acute phase sera were 4.0 (CF) and 8.3 (HI).

Comment

Numerous investigators have commented on the value of the complement-fixation test in the diagnosis of epidemic influenza.[6-10] Not only are difficulties in interpretation of the HI test due to viral strain differences avoided, but the titer of CF antibody in normal human sera is low and levels are significantly elevated shortly after the onset of disease. In the spring phase of the epidemic, twice as many positives were detected by the use of the CF test as with the HI test. Furthermore, 79% of 204 positive convalescent sera showed an increment in titer of eightfold or greater by CF.[11]



Group 2. Fold increase of titer in convalescent sera as compared with the CF and HI titer of acute-phase sera (number of samples in parentheses).

Though the number of patients in Group 2 was small, the results were statistically significant. Maximal titers of CF antibody occurred 2-3 weeks after onset of disease, declining to low levels by the 20th week. This agrees with findings in adults reported previously.[10-14] The Far East strains retain the "soluble" CF antigen common to other Group A influenza viruses, and so this response to infection in a young military population is not unexpected.

Previous studies have shown that CF, HI, and neutralizing antibodies to influenza develop early and in parallel, maximal titers occurring two to three weeks after onset of illness.[12-14] Maximal titers of HI antibody were found not in the third-week specimens but in the six- to seven-week period. Although the earliest period of maximal response can not be determined from the data, there is a significant delay in HI antibody compared to the development of CF antibody. This delay may account for the

relatively poor results obtained with the HI test when convalescent specimens were collected before the 21st day. It is unknown whether the antigenic "novelty" of Far East-influenza viruses is responsible for this phenomenon.

Summary

The hemagglutination-inhibition and complement-fixation antibody response in military personnel to "Far East" influenza virus is described. The CF test was of value in the early diagnosis of epidemic influenza, as a rise in titer occurred by the second week of illness. HI antibody appeared at maximum values after the third week of illness. This response is at variance with previous observations.

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Relationship Between Red Cell and Plasma Volume During Recovery from Pernicious Anemia

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Introduction

The disparity between the subjective improvement, the reticulocytosis, and the increase in hematocrit early in the course of treatment of pernicious anemia has been observed but is incompletely understood.[1,8] In view of the prompt clinical improvement and early reticulocytosis it seems probable that the lag in hematocrit response does not indicate delayed hematologic improvement but more likely indicates a proportionate increase in plasma volume during the initial response of the red cell volume, and so the hematocrit is little affected.

Despite studies by many workers on blood volume in pernicious anemia, no characteristic abnormal pattern in this disease has been established. Consequently, no suitable explanation for the lag in rise of the hematocrit has been obtained.

Review of Literature

Smith,[2] in 1900, studied seven cases of pernicious anemia and, using a carbon monoxide absorption and dilution method, found the blood volume to be normal or even elevated. Lindeman, in 1918, using a method based on changes in hematocrit following rapid transfusion of known volumes of blood,[3] observed the blood volume to be extremely low in 7 of the 10 patients studied.[4] Keith,[5] in 1923, employing a dye-dilution technique, demonstrated normal or elevated plasma volumes in each of his 12 patients with pernicious anemia. Gibson,[6] in 1939, also employing the dye-dilution method (Evans blue dye [T-1824]), found no significant changes from the predicted normal in his patients before treatment and no consistent alteration of blood volume during the first several months after treatment. Hallberg,[7] in 1955, utilizing a method dependent on endogenous formation of carbon monoxide, reported great variation in blood volume in individual cases. In addition, he noted that as the red cell volume increases there is a compensatory decrease in plasma volume, with maintenance of a nearly constant total blood volume. Meyer and Bertcher,[8] in 1952, employing dilution of erythrocytes tagged with radioactive phosphorus (P^{32}), observed one patient who had a low total blood volume and three patients who had normal blood volumes. These investigators were the first to seek an explanation for the frequently delayed rise in hematocrit despite prompt reticulocytosis, but their four cases failed to exhibit this phenomenon, and they abandoned the project.

The inconclusiveness of the above-described studies led us to investigate the response of total blood volume and red cell volume during initial treatment of three severely ill patients with pernicious anemia. These data are the basis for the following report.

Methods

The diagnosis of pernicious anemia was based on typical abnormalities of the peripheral blood and bone marrow, on the presence of histamine-fast achlorohydria, and on the Shilling test,[12] which was performed at the completion of the study. The diagnosis was confirmed in each case by the response to therapy with cyanocobalamin (vitamin B_{12}).

Blood-volume studies were performed by a modification of the methods described by Sterling and Gray[9] and by Read.[10] Approximately 25μc. of Cr^{51}

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Vanderbilt University School of Medicine.

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TABLE 1.—*Laboratory Findings in Three Cases of Pernicious Anemia*

	Case 1						Case 2						Case 3					
Hosp Day	PCV, %	Retic., %	RBC Vol., Ml.	Plasma Vol., Ml.	Total Vol., Ml.	B_{12}, μg.	PCV, %	Retic., %	RBC Vol., Ml.	Plasma Vol., Ml.	Total Vol., Ml.	B_{12}, μg.	PCV, %	Retic., %	RBC Vol., Ml.	Plasma Vol., Ml.	Total Vol., Ml.	B_{12}, μg.
1	22	0.2				50	25	0.2					26	1.4				
2	23		500	1,775	2,275	50	24		490	1,560	2,050	0.25	25					
3						50						0.25	24	2.8				
4	21.5	0.2				50	25	1.0	675	1,925	2,600	0.25	24	3.5	875	2,540	3,500	1,000
5						50		1.3				0.25	25					
6	20	1.4	690	2,410	3,100	50						0.25	24.5	4.2				
7	20					50	29	3.6	875	2,150	3,025	0.25	25	7.3	1,050	3,050	4,100	
8	20		860	3,440	4,300	50		3.3				0.25	25	8.3				
9	20	8.1				50		8.7				0.25	26	5.0				
10	20	7.4	920	3,680	4,600	50	30	11.9	1,020	2,380	3,400	0.25		4.2				
11		6.9				50		9.0					29	5.0	1,180	2,820	4,000	
12						50		9.4					30	2.0				
13	21	3.0	1,100	3,700	4,800	50	34		1,040	2,010	3,050	0.25						
14						50						0.25	30		1,140	2,660	3,800	1,000
15	27	5.0	1,100	2,900	4,000	50						0.25	29	2.1				
16	26	4.9				50						0.25						
17	27	4.4	1,140	3,060	4,200	50	35		1,020	1,880	2,900	0.25						
18	27	2.4				50		5.3				0.25						
19						50						0.25						
20	30	1.9	1,380	3,220	4,600	50						0.25						
21	28	5.1				50						0.25						
22	30	2.4				50	35	2.2				0.25						
23						50						0.25						
24	30		1,230	2,870	4,100	50						0.25						
25						50	35	0.9				0.25						
26						50						0.25						
27	31	1.0				50	39		1,180	1,820	3,000	0.25						
28						50						0.25						
29						50						0.25						
30						50						0.25						
31	34	1.3	1,420		4,100	50						0.25						
32												0.25						
33							40		1,250	1,875	3,125	0.25						

Predicted Normal Values

Case	RBC Vol., Ml.	Plasma Vol., Ml.	Total Vol., Ml.
1	1,900	2,700	4,600
2	1,900	2,700	4,600
3	2,100	3,100	5,200

TABLE 2.—*Plasma Protein Levels*

	Before Treatment			After 1 Mo. of Treatment		
Case	Total, Gm. %	Albumin, Gm. %	Globulin, Gm. %	Total, Gm. %	Albumin, Gm. %	Globulin, Gm. %
1	5.8	3.6	2.2	6.6	4.0	2.6
2	6.8	4.2	2.6	6.6	4.2	2.4
3	5.6	3.5	2.1	6.2	3.8	2.4

was injected for each determination. Thirty minutes was allowed for complete mixing before the final sample of blood was withdrawn from the opposite arm. Duplicate samples were counted in a well type scintillation counter. In this laboratory the red cell volume has been found to be reproducible to ±4% in two subjects, with 10 separate determinations in each. Hematocrit determinations (Wintrobe) were made in duplicate on blood samples drawn 30 minutes apart. The red cell mass was calculated from the total blood volume and the hematocrit. Occasional plasma-volume estimations were performed by dilution of Evans blue dye, with 10 minutes being allowed for mixing of the dye before the final blood sample was obtained. The predicted normal values for total blood volume in these patients was obtained from the chart by Gibson and Evans, based on square meters of body surface.[11] Reticulocyte counts were performed by the method of Wintrobe.

Results

The three patients were all severely anemic before treatment, and all exhibited blood volumes that were about one-half of the predicted normal value. The red blood cell volume was even more severely depressed, with about one-fourth of the predicted value being initially demonstrated.

During cyanocobalamin therapy there was prompt subjective clinical improvement, and by the fourth day reticulocytosis was well established. Progressive and almost linear increases in red cell volume were noted during the first two weeks. Thereafter these increases were of less magnitude but were still demonstrable. Plasma volumes increased promptly and during the first week restored the total blood volume to normal. Subsequently, the plasma volumes fell slightly. Ultimately all cases had complete hematological recovery. The data are presented in Table 1 and in the following description of cases.

CASE 1 (Fig. 1).—The patient, a 73-year-old woman, had a body-surface area of 1.6 square meters (height, 165 cm.; weight, 59 kg.) and a predicted blood volume of 4,600 ml. Her initial blood volume was 2,275 ml., and her red cell volume was 500 ml. During the first 13 days of treatment her blood volume (and plasma volume) increased progressively until a normal total volume was obtained. In this period the hematocrit did not vary appreciably from the 20% observed on admission. In the second and third weeks the plasma volume actually diminished somewhat, while the red cell volume continued to increase. In keeping with this change the hematocrit showed regular

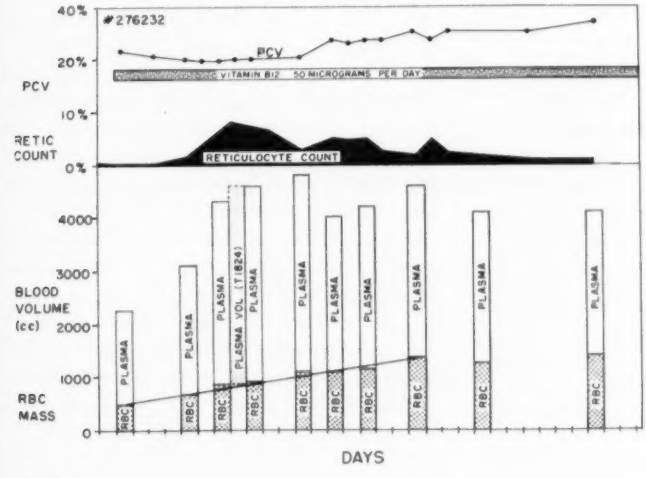

Fig. 1.—The course of a 73-year-old woman during treatment of pernicious anemia. The plasma volume and red cell volume increased promptly and in such proportion that the hematocrit did not increase until the 14th day.

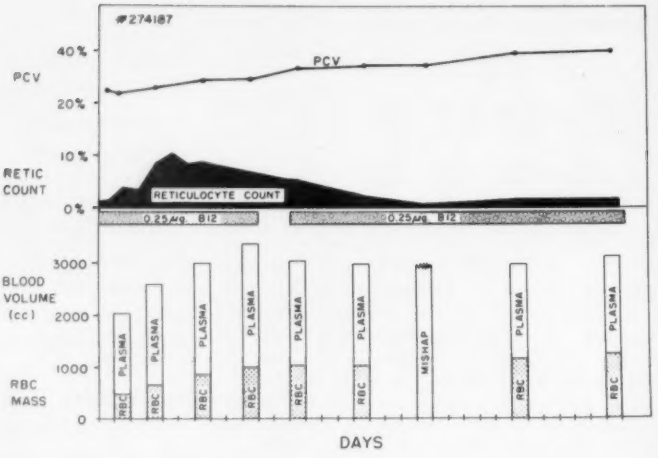

Fig. 2.—The course of a 70-year-old man during treatment of pernicious anemia, showing prompt rise in red cell and plasma volume with delay in elevation of hematocrit.

increases in proportion to the enlarging red cell volume.

CASE 2 (Fig. 2).—The patient, a 70-year-old Negro man, had a predicted normal blood volume of 4,600 ml. (height, 167 cm.; weight, 58 kg.; body surface, 1.6 square meters). His initial blood volume was 2,100 ml., and his red cell volume was 480 ml. Although not so pronounced in Figure 2, it is apparent in Table 1 that his hematocrit did not increase significantly until the end of one week of treatment, by which time the plasma volume had nearly reached its peak value. Thereafter the hematocrit rose steadily with the enlarging red cell volumes.

CASE 3 (Fig. 3).—The patient, a 73-year-old man, had a predicted blood volume of 5,200 ml. (height, 180 cm.; weight, 66 kg.; body surface area, 1.8 square meters). His initial total blood volume was 3,500 ml., with a red cell volume of 875 ml. With treatment the red cell volume increased progressively, but not until the 11th day did the hematocrit increase significantly.

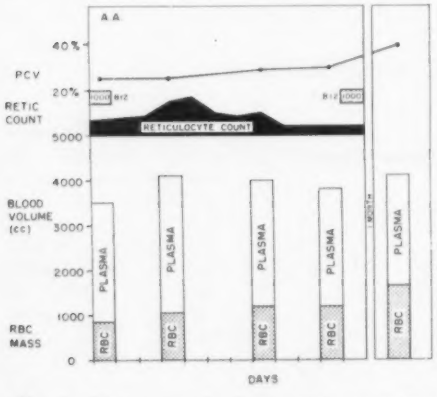

Fig. 3.—The course of a 73-year-old man during treatment of pernicious anemia. There was less severe anemia than in Cases 1 and 2, but similar blood-volume changes are present.

In these patients, the plasma protein levels were normal prior to treatment, and subsequent determinations made one month later showed no significant change. Serial determinations of the plasma proteins were not performed.

Comment

These three patients, who were severely ill with pernicious anemia and who had initial blood volumes of only about one-half of normal, demonstrated a consistent pattern of response to treatment. The initial increase in both plasma and red cell volume was so nearly proportional that significant changes in hematocrit did not occur early in treatment. These patients had in turn low, normal, and, later in two of the three cases, slightly above-normal blood volumes. If one can assume that patients in relapse exhibit the reverse sequence as they become anemic, the conflicting reports of low, normal, or occasionally slightly elevated blood volumes in untreated pernicious anemia can be explained by the stage of the illness studied. During therapy patients might show increase in total blood volume or no significant change in total volume, depending upon

the severity of the illness at the time therapy is begun. The observation of Hallberg[7] that the plasma volume decreases as red cell volume increases, with maintenance of a nearly constant blood volume, is confirmed with the reservation that this is true only after the blood volume has returned to normal.

The concomitant and proportional increases in plasma and red cell volume during the first few days of treatment explains the frequently observed lag in rise of the hematocrit. This delay in elevation of hematocrit should be most pronounced in severely ill patients.

This study also raises the interesting question as to the role of cyanocobalamin in production of plasma. This effect might well be direct, since the plasma volume increases so promptly and actually reaches normal (and above normal) within two weeks, long before the red cell volume is restored.

Summary

In three cases of pernicious anemia, the untreated state was characterized by a low red cell volume and a low plasma volume. Treatment was followed by prompt clinical improvement and a rapid increase in total blood volume. The hematocrit remained essentially unchanged during this time because of dilution of the increasing red cell volume by the increasing plasma volume. After about one week the total blood volume stabilized at near normal values, while the red cell volume continued to increase. During this latter period the hematocrit rose steadily in proportion to the increasing red cell volume. Complete hematological recovery with restoration of normal hematocrit and red cell volume required about two months.

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Case Reports

The Successful Medical Management of a Phytobezoar

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It has been our contention that an obvious discrepancy exists between the number of persons who eat persimmons and the occasional case of bezoar which produces distressing symptoms. This is especially true in an area indigenous to persimmon ingestion, such as Kansas, Oklahoma, and southern Nebraska.

It is the usual procedure to institute surgical intervention when a patient has severe distress resulting from a persimmon bezoar. This observation stimulated our interest, and so a case of persimmon bezoar was placed on medical management and then followed serially for radiological proof of elimination of the last remnant of the bezoar.

The method of treatment and its effect upon persimmons was studied in vivo as well as in vitro. The results suggest that a case of bezoar detected early may be amenable to medical management.

Report of Case

A 72-year-old white woman was admitted to The Menorah Medical Center on Oct. 28, 1957, with the chief complaint of severe abdominal cramping followed by nausea and vomiting.

She stated that 24 hours prior to admission she had eaten approximately two dozen persimmons. That evening she awakened at 12 o'clock, with epigastric pain, cramping in nature, followed by vomiting. She took Gelusil (an antacid absorbent) and glutethimide (Doriden), 0.5 gm., and was unable to obtain any relief from the severe nausea and cramping pain. She was then seen by her physician, who admitted her to Menorah Hospital.

Past History.—She has been a long-standing hypertensive, cardiovascular patient under orthodox treatment for hypertension and chronic cardiac decompensation. Blood pressure has been only fairly well controlled, but compensation has been adequate.

Physical Examination.—She was well developed and moderately nourished, but in acute distress. Eye, ear, nose, and throat examination revealed a Grade II retinopathy. The heart revealed moderate cardiomegaly. The BP was 190/70; pulse, 84. There was a soft systolic murmur at the apex.

Abdomen.—The liver was down 2 fingerbreadths. There was moderate distention of the abdomen, with encreased borborygmi. The epigastric area was tender to palpation, and several irregular masses could be palpated in the epigastrium. The remainder of physical examination was noncontributory.

Hospital Course.—Since a history of persimmon ingestion preceded her discomfort, an upper gastrointestinal examination was requested, along with interval studies. On Oct. 29 (Fig. 1), the x-ray study revealed a diffuse irregularity of the stomach outline, with multiple areas of radiolucency observed within the gastric lumen. The size of the shadows varied from 1-2 cm. to 5-6 cm. in greatest diameter. The mucosa of the stomach was not involved with the "pseudotumors," and there was freedom in movement of the shadows within the stomach. The diagnosis of bezoar was supported by the roentgen study.

Since the patient was considered a poor surgical risk in light of her heart status, a medical program utilizing a papain-Na bicarbonate powder was proposed. This was prepared in 0.5 gm. quantities, which were given to the patient in a glass of water every three hours. The stomach was rechecked by x-ray on Nov. 11 (Fig. 2) and again on Nov. 23 (Fig. 3). During these subsequent examinations there was a definite reduction in the number and size of the bezoars, until on

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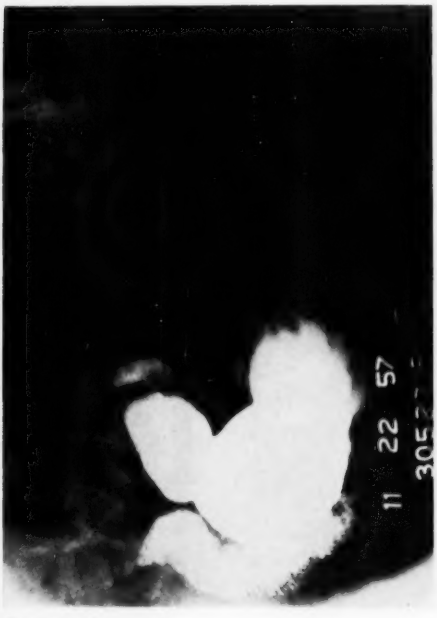
From the Menorah Medical Center; Radiologists (Drs. Dann and Rubin), Department of Internal Medicine (Dr. Passman), Resident in Medicine (Dr. Deosaransingh), Resident in Radiology (Dr. Bauernfeind), and Director of Biochemistry (Dr. Berenbom).

Fig. 1 (Oct. 29, 1957).—Stomach examination demonstrates the multiple radiolucent shadows of varying size filling the gastric lumen and producing some distention.

Fig. 2 (Nov. 11, 1957).—Decrease in the radiolucent shadows filling the stomach.

Fig. 3 (Nov. 23, 1957).—A normal appearance of the stomach outline, with no residual foreign bodies.



the final examination date no bezoars were detected in the stomach.

Comment

The earliest case of phytobezoar is credited to Bucknill and was reported by Quain,[12] in 1854. He stated that the mass observed in the stomach was composed of string and coconut fibers. It is of dialectic interest that foreign bodies have been recognized to exist in the stomach as early as the 12th century B.C. Early medical literature referred to the vegetable fibers that may remain undigested in humans, simulating the situation found in ruminants.

Bezoars are most frequently formed from vegetable matter or hair. The phytobezoar is derived from the vegetable, but persimmons appear to be the most frequent cause. Other substances that have been accused are wood fiber, beets, parsley-like plants, etc.

The surgical alleviation of phytobezoars due to persimmons or other vegetable fibers has heretofore been a foregone conclusion. This is emphasized in the literature, where

over 400 cases have been recorded, and in each case surgery was the treatment prescribed.

A close scrutiny of the literature reveals that several observations are evidently responsible for excluding medical management as a possible method for accomplishing any dissolution of the bezoar. Thus, Droegemueller [10] and Smith [11] recorded two cases in which the bezoar existed for several years and possibly longer. This report was based on the history of the patient as related to the chronic history of epigastric pain. It is difficult to discern in either case whether persimmons were ingested on several occasions or whether a single episode of eating them antedated the findings.

In other cases the average time from ingestion to discovery of the condition has been 120 days.

Other observations that have favored a surgical approach are the report on the biochemistry of the bezoar and Chont's analysis [3] of the formation of the mass. He has shown that persimmons, when not fully ripe, will form bezoars in a solution of decinormal HCl with or without pepsin but not in water or an alkaline solution. The astringent in persimmons is shibuol or phlobotannin composed of phloroglucin and gallic acid. This material in the gastric acid transforms the fruit into a sticky coagulum, insoluble shibuol, thus producing a ball.

Subsequent to the apparently successful management of the persimmon bezoar with papain we conducted experiments in vitro on the ability of papain, pepsin, and their combination to dissolve persimmons. Unfortunately, it was difficult to obtain the fruit by the time these experiments were set up, so the data are really preliminary, but useful.

A suspension of persimmon was prepared by homogenization in a Waring Blendor in 0.1 M acetate buffer, pH 4. To four equal aliquots of this suspension were added 20 mg. each of papain, pepsin, papain-pepsin, papain-pepsin-Pluronic F. These additions were repeated at 48-hour intervals for one week, the suspension being kept at 37 C. A control tube containing only the suspension was also carried along. Photographs were taken at the beginning of the experiment, at which time pictures were taken of the suspension upon its removal from the incubator and two and five minutes after shaking to resuspend the homogenate and note the rate of sedimentation. These are shown in Figure 4. The conclusion from this experiment, illustrated in the photographs, was that papain was the most effective single component in causing the persimmon suspension to break down to

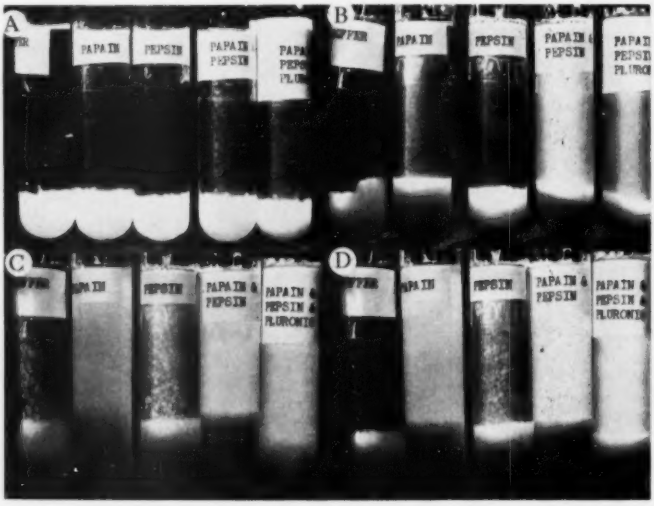


Fig. 4.—Action of enzymes on persimmon suspensions at pH 4.0 *A*, suspensions at start of experiment. From left to right, the tubes contained buffered suspension, suspension plus papain, suspension plus pepsin, suspension plus papain-pepsin, and suspension plus papain-pepsin-Pluronic-F. *B*, same as *A*, one week after incubation at 37 C. *C*, same as *B*, two minutes after mixing and allowing suspension to settle by gravity. *D*, Same as *B*, five minutes after shaking.

finer particles; the rate of settling of particles was slower in the tube containing papain than in the one containing pepsin or buffer only and as slow as in the tubes containing combinations of papain and pepsin. None of the combinations was more effective. The degree of "solution" appears to be very slight, but the important observation seems to be that papain is able to effect disintegration of large particles and if obtained in the stomach would assist in the reduction of bezoars to particles of a size suitable for passage into the intestine, where further enzymatic breakdown would occur.

Nitrogen analysis of the persimmon suspension indicated that a very small proportion of this fruit is protein. One would, therefore, not expect proteolytic enzymes to "dissolve" persimmon bezoars. One could speculate that the protein in the bezoar is effective as a "bridge" cement substance, helping to keep the bezoar in the form of a large mass. Proteolytic activity, in which papain is more effective than pepsin, might then dissolve the "bridges," enabling the peristaltic action of the stomach to reduce the bezoar to a suspension of fine particles.

The belief is also held that the prolonged use of papain on a daily basis, providing an almost constant supply of enzyme, was an additional reason for the success of this treatment in the present case, since it was found that disintegration of the bezoar was a gradual process. It would be interesting at some future date (circumstances did not permit it here) to determine if the cessation of papain administration would result in arrest of bezoar disintegration.

Summary

A case is reported with the intention of suggesting early medical management for the treatment of a persimmon phytobezoar. Papain-Na bicarbonate powder was administered every three hours until the bezoar disappeared. Radiological as well as experimental evidence is offered to demonstrate the effect of papain on persimmon bezoars.

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The Nephropathies of Sickle-Cell Disease

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Many of the complications of sickle-cell anemia have been well described and may be readily diagnosed, e. g., the pulmonary and cardiac manifestations.[1,2] In contrast, the functional and morphological renal changes associated with hemoglobin S have received little intensive study until the past few years. Margolies, in a clinical and pathologic review of the subject in 1951, mentioned albuminuria, hematuria, cylindruria, frequent urinary infections, fixed specific gravities, uremia and renal thromboses, and infarctions as complications of sickle-cell disease and trait.[3] The nephropathies thus far described in detail include gross hematuria,[4] hyposthenuria,[5] fat embolism,[6] and the nephrotic syndrome.[7]

The referral of a patient with homozygous hemoglobin S and massive proteinuria provided the opportunity to observe many of these renal defects in the same subject and to study their response to corticotropin (ACTH).

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Report of Case

The patient was a 9-year-old Negro boy with eight hospital admissions preceding the present one. The significant features were as follows:

1949—irritability, vomiting, coughing, hepatic and splenic enlargement, anemia, positive sickle preparation.

Results of Blood and Urine Examinations Compiled from Hospital and Outpatient Records, 1949—1958, in a Nine-Year-Old Boy with Sickle-Cell Anemia

	Urine			Blood				
	Sp. Gr.	Protein	Formed Elements	BUN, Mg/100 Ml.	TP Gm/100 Ml.	A/G	Cholest. Mg/100 Ml.	HB., Gm/100 Ml.
1949		Neg.	Occ. granular cast					
1951	1.023	Neg.	Occ. WBC		6.0	4.2/1.9		8.8
1952	1.012-1.014	Trace to ++	Rare WBC to clumps WBC					
April 1956	1.005	2+	Rare WBC cast; rare RBC; rare hyaline cast; many WBC					
July 1956	1.001	3+	Few WBC; occ. gran. cast	9	6.3	3.2/3.1		8.5
Aug. 1956	1.005-1.009	4+	Many bacteria; few RBC	12	4.7-5.8	2.4/2.3, 2.8/3.0	275-330	8.5
Nov. 1957	1.005-1.012	4+	WBC, bacteria; few gran. cast; occ. hyaline cast	14	5.9-5.0	3.5/2.4, 3.0/2.0	220-250	7.0
1958	1.005-1.014	4+	5-8 WBC/hpf; occ. clump WBC; freq. hyaline & gran cast + DRFB *	8	4.7	1.1/3.6	260-440	7.5

* Doubly refractile fat bodies.

1951—swelling and pain in left hand.

1952—abdominal and extremity pain, cardiomegaly, balanitis.

1952—pain and swelling of the left leg.

1956, March—leg pain, vomiting, gross hematuria, liver and spleen progressively more enlarged, blood pressure 90/60.

1956, August—anorexia, jaundice, bilirubinuria, diagnosed as serum hepatitis.

1957—abdominal and extremity pain, fever, proteinuria (7.5 gm. per day).

Urine examinations and other laboratory work are presented in the Table. Failure to concentrate random urine samples, proteinuria and pyuria have all been present since age 3.

The patient was readmitted for study in January, 1958. Physical examination revealed an alert intelligent boy with an extremely protuberant abdomen, 49 in. (124.5 cm.) tall, and weighing 56 lb. (25.5 kg). The heart, liver, and spleen were enlarged; the blood pressure was 120/80. The legs were free of ulcers, and there was no edema. The nail beds were pale but otherwise normal.

Initial laboratory studies showed a hematocrit of 26% and a corrected sedimentation rate of 20 mm. in one hour. The serum total protein was 4.7 gm. per 100 ml., with an A/G ratio of 1.1:3.6; serum cholesterol varied from 260 to 400 mg. per 100 ml.; serum sodium was 143 mEq. per liter; 24-hour urine proteins ranged from 9.2 to 15.4 gm., of which 58% was albumin on electrophoretic analysis. Examination of the urine revealed doubly refractile fat bodies, hyaline and granular casts, and 5-8 white cells per hpf. with clumps. Specific gravities were from 1.011 to 1.014, with reactions of 5.0 to 6.0. Urine culture showed a hemolytic Staphylococcus pyogenes var. aureus, coagulase-positive.

Methods

The patient was ambulatory and eating a regular ward diet containing approximately 170-190 mEq. of sodium. Twelve- or twenty-four-hour urines were collected at intervals throughout the study.

DAYS 1 and 2.—Eighteen hours of total dehydration, with endogenous creatinine clearances and urine and plasma osmolalities determined during each of the last two hours. Urines were collected by an indwelling catheter. A 15-minute P. S. P. excretion test followed the clearance periods.

DAY 4.—Right kidney biopsy done under general anesthesia through a flank incision (Dr. Timothy Kelly). Procedure followed by extremity pain and fever for 36 hours.

DAY 15.—Water loading, urine flow 3.5 ml. per minute. One unit of previously assayed vasopressin (Pitressin, Parke, Davis & Company) given intravenously, with measurements of urine and blood osmolality at 20-minute intervals for 60 minutes.

DAY 17.—Corticotropin begun, 40 units intramuscularly twice daily for two days, then 20 units twice daily for 13 days.

DAY 31.—Creatinine clearances, and response to vasopressin during water loading measured as before.

Chemical determinations on blood and urine were done by standard laboratory methods. Twenty-four-hour urine proteins were measured by the method of Shevky and Stafford.[8] Urine and plasma osmolality was determined by the freezing-point method, with use of a Bowman apparatus manufactured by the American Instrument Company. The corticotropin used was repository corticotropin injection, made by Organon, Inc.

Results

Figure 1 depicts the over-all plan of study together with the specific measurements. The results prior to corticotropin administration included a normal endogenous creatinine clearance and a nearly normal 15-minute P. S. P. excretion. Urine protein excretion exceeded 9 gm. per day, while urinary sodium concentrations averaged 73 mEq. per liter, with daily outputs approximately equal to intakes. The highest urine-to-plasma osmolal ratio observed with

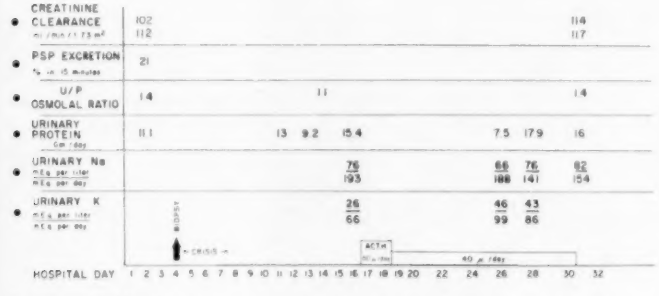

Fig. 1.—Plan of study and results of corticotropin administration in a patient with sickle-cell anemia and the nephrotic syndrome.

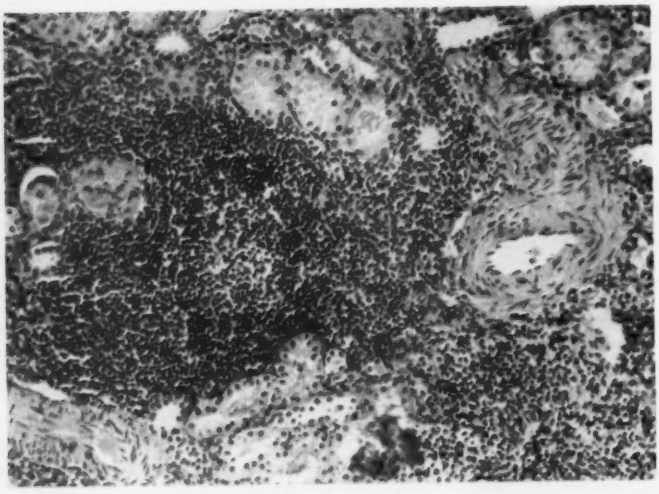

Fig. 2.—Renal biopsy in sickle-cell disease; far-advanced pyelonephritis with nephrosclerosis; reduced 40% from mag. × 110.

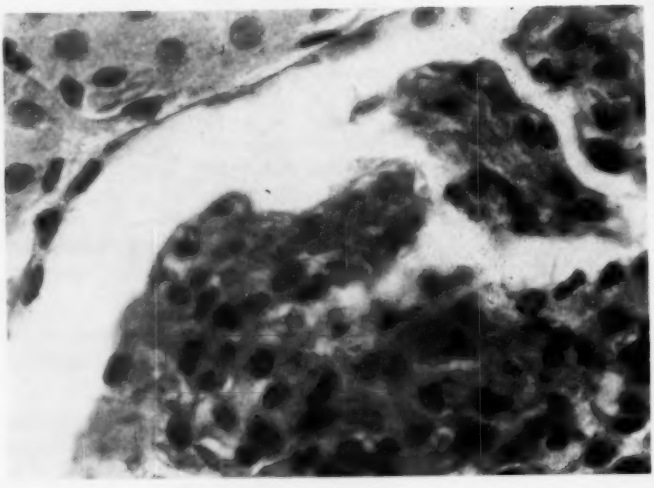

Fig. 3.—Renal biopsy in sickle-cell disease; glomerular capillary stuffed with masses of sickled red cells; reduced 40% from mag. × 700.

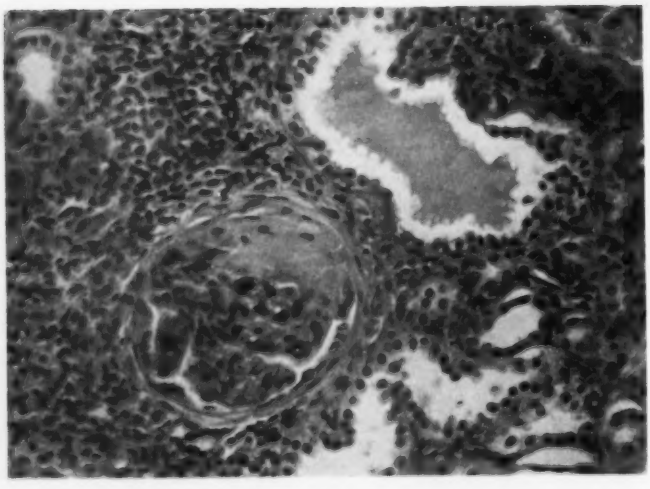

Fig. 4.—Renal biopsy in sickle-cell disease; focal glomerular hyalination and pyelonephritis; reduced 40% from mag. × 205.

dehydration and vasopressin was 1.4. Fifteen days of corticotropin administration produced no significant changes. Electrophoretic analysis of serum and urine protein revealed only the abnormalities to be found in the nephrotic syndrome of many etiologies.

The renal biopsy presented an extremely variegated picture. Areas of normal tissue were interspersed with areas of far-advanced pyelonephritis (Fig. 2). Glomeruli varied from normal to completely hyalinized. Many were distended with masses of sickled red cells (Fig. 3); a few showed focal hyalination (Fig. 4).[7] Other glomerular changes including marked membranous thickening, epithelial proliferation, and occasional necrosis. Arteriolsclerosis was seen in the areas of pyelonephritis. Special stains failed to reveal the presence of fat.

Comment

Although all of the usual criteria[9] for the diagnosis of the nephrotic syndrome were present except edema, this patient's rate of protein excretion and the presence of doubly refractile fat bodies in the urine were, in themselves, sufficient for the diagnosis.[7] This is the third published instance of a nephrotic syndrome in sickle-cell anemia and the first to be treated with corticotropin. The transient decrease in proteinuria during corticotropin administration cannot safely be ascribed to treatment, since nephrotic patients may spontaneously demonstrate as much variation in their protein excretion rates. The urinary sodium concentrations and daily excretions were unusually high for the nephrotic syndrome and did not change during treatment with corticotropin. The possibility may be entertained of a sodium-transport defect as part of this patient's nephropathies.

The glomerular lesions revealed by the renal biopsy provide an adequate histologic background for the patient's nephrotic syndrome. The manner in which sickle-cell anemia produces glomerular alterations is not clear. Focal thromboses, stagnant anoxia, and the possibility of toxic properties of plasma hemoglobin S may be considered. Such obviously irreversible glomerular damage as this patient showed would not be expected to respond to corticotropin.

The patient's response to endogenous antidiuretic hormone and administered vasopressin was grossly impaired as judged by the urine-to-plasma osmolal ratios. Normal subjects may be expected to develop ratios of more than 3.5:1 under similar circumstances. Admittedly, we have not proved that our patient's concentrating defect is related to his hemoglobinopathy (i. e., by reversing it with multiple transfusions); however, the presence of a normal creatinine clearance and P. S. P. excretion and the absence of any other obvious reason for a failure to respond constitute satisfactory indirect evidence. The mechanism of the hyposthenuria is unknown and cannot be clearly correlated with any of the histologic changes found. The history of gross hematuria likewise could not be correlated with the biopsy. Mostofi has shown that bleeding usually occurs from lesions in the papillae and subpelvic mucosa, areas not usually seen in biopsy material.[4]

Certain other aspects of this case merit comment. The insidious course of pyelonephritis remains poorly appreciated, in spite of a large recent literature dealing with the subject. A presumptive diagnosis of pyelonephritis should be made whenever a predisposing factor and pyuria are found in the same patient, regardless of the clinical picture. The predisposing factors here were the presence of severe parenchymal renal disease with distortion of nephron architecture and, of less importance, the recurrent balanitis. The value of renal biopsy in delineating the histologic features of a particular patient's nephrotic syndrome is well demonstrated, as is the possibility of diagnostic error involved in merely assuming an etiology (e. g., poststreptococcal glomerulonephritis).

The frequency of the various sickle-cell nephropathies will vary with the extent of the diagnostic procedures employed. Cer-

tainly, careful urine examinations and quantitative protein excretion measurements are within the reach of all who treat hemoglobinopathic patients.

Summary

A 9-year-old Negro boy with sickle-cell disease was demonstrated to have the nephrotic syndrome. There were in addition multiple glomerular lesions, pyelonephritis, a vasopressin-resistant concentrating defect, and gross hematuria (by history). Corticotropin (ACTH) administration was without significant effect.

Dr. Paul McCurdy, of the District of Columbia General Hospital, made the hematologic determinations, and Miss Phyllis Straub, the chemical analyses.

Georgetown University Medical Center, Georgetown University Hospital (7).

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Cystic Fibrosis of the Pancreas in a Young Adult

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Cystic fibrosis of the pancreas is a hereditary disorder giving rise to symptoms in infancy and childhood in the great majority of cases. A recent review of a series of 397 patients seen in the past 17 years reported that less than 9% were above the age of 10 years.[1] The oldest patient being followed in the series was 22 years of age. It is well known that the severity of the pulmonary involvement in the disease is commonly responsible for death, which usually occurs in early childhood. Despite this, several reports attest to the fact that an occasional child with cystic fibrosis of the pancreas may live to become a young adult with the aid of intensive therapy.[2-4] There are only a few reports of isolated cases in which the disease was first diagnosed in late adolescence or early adult years.[5,6] The present case of a young man with cystic fibrosis of the pancreas, in whom the diagnosis was first established when he was 18 years of age, is reported because it falls into this small and unusual group.

Report of Case

The patient was a white boy, 18 years of age at the time of his admission to the Medical Service of the University Hospitals. His chief complaints on admission were shortness of breath and a productive cough, which had been worse in the past two months, though the symptoms had been present for as long as he could remember.

Apparently he was well at birth, but soon his mother became aware that his stools were bulky and foul-smelling. He was breast-fed during the first few months of life. Aside from the abnormality of the stools he had no difficulty at that time. He was troubled several times with rectal prolapse about the age of 6 years. On several occasions in early childhood the patient was treated for asthma because of nonproductive cough and wheezing respirations. These episodes had no seasonal variation. The patient received no prolonged treatment with antibiotics during these early years.

Shortness of breath had always prevented the patient from engaging in athletic activities. He had a small amount of hemoptysis on three occasions following vigorous exertion in the past three years. He was able to attend school regularly, however, and to work during the summer at odd jobs. He never noted any particular intolerance to heat. His appetite was always very good.

In August, 1957, he had a febrile illness characterized by increased cough. This was diagnosed as pneumonia and treated with antibiotics. After this there was much improvement in his shortness of breath and coughing. Because of the abnormalities in the roentgenograms taken during this illness and the duration and severity of his symptoms the patient was referred for evaluation.

Family History.—There had been seven children in the family. Two had died; one at the age of 6 months, with severe diarrhea, and the second at the age of 6 years, of measles complicated by pneumonia. The mother reported that both of these children had stools that were bulky, very foul-smelling, and different from those of any of her other children except the patient.

Physical Findings.—The patient was a thin somewhat undernourished youth whose abdomen was slightly protuberant. His weight was 125 lb., and his height was 70.5 in. He did not appear emphysematous and was in no respiratory distress. There were scattered fine rales on inspiration throughout both sides. No wheezing was heard. The cough was productive of a small amount of thick greenish mucus. The heart was normal. The liver was felt 4 cm. below the right costal margin in the midclavicular line. It was firm, smooth, and nontender. The spleen was not palpable. Severe clubbing of the fingers and toes was present. The patient was not cyanotic.

Laboratory Findings.—The concentration of hemoglobin was 12 gm. per 100 ml. with a leukocyte count of 9,600 per cubic millimeter and a differential count of 3 band forms, 55 polymorphonuclear cells, 41 lymphocytes, and 1 monocyte. The urine

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Figure 1

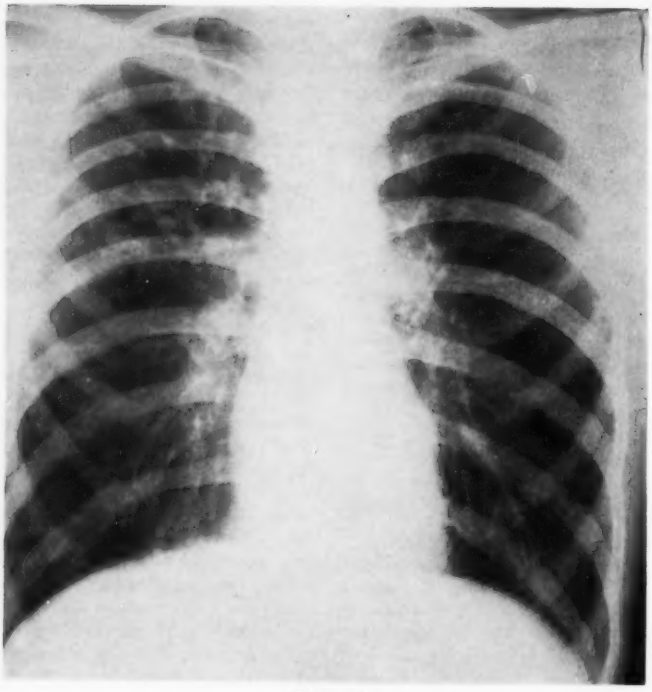

Figure 2

Figure 3

was normal. Culture of the sputum showed that Staphylococcus pyogenes var. aureus was the predominant organism. Culture of the sputum for tubercle bacilli was negative. Skin tests for tuberculosis and histoplasmosis were negative.

Roentgenograms of the chest showed peribronchiolar infiltration, most pronounced in the right upper lobe. There was moderate generalized emphysema and a few areas of focal atelectasis and emphysema. Hilar markings were much increased. Linear streaking in the left apex suggested fibrotic changes (Fig. 2). Bronchograms confirmed the impression of bronchiectasis in the right upper lobe.

Studies of pulmonary function are recorded in Table 1. The vital capacity was normal, but the residual volume was increased. There was evidence of uneven distribution of inspired air, a large physiologic dead space, and some reduction in the mechanical function of the lungs. These studies showed no evidence of pulmonary insufficiency as regards oxygenation of the blood and elimination of carbon dioxide.

An electrocardiogram was normal.

Stools were bulky, foul-smelling, and greasy. Duodenal intubation to obtain fluid for analysis of proteolytic activity was attempted on two occasions without success. An indirect test of digestion and absorption with use of olein labeled with I^{131} was performed. After a 12-hour fast, the patient was given a homogenized meal containing olein. Radioassay of stools collected for the next four days revealed that 19.1% of the olein was excreted (normal, less than 5%). The maximal plasma radioactivity, expressed in terms of the total plasma volume, was 2.3% of the administered dose (normal 8.5%±1.9). A vitamin A tolerance curve was abnormally low, with values of 28μg., 28μg., 33μg., and 28μg. per 100 ml. for the fasting and 4-, 9-, and 24-hour values, respectively (normal minimum, 40μg. per 100 ml.). The administered dose was 1,000 units of vitamin A in oil per kilogram. The concentration of carotene in the serum was 20μg. per 100 ml. (normal minimum, 100μg. per 100 ml.).

Sulfobromophthalein (Bromsulphalein) retention was 2%, and alkaline phosphatase was 4.2 Bodansky units. The concentration of protein in the serum was 5.7 gm. per 100 ml., with 3.5 gm. of albumin and 2.2 gm. of globulin per 100 ml. The concentration of bilirubin in the serum was 0.4 mg. per 100 ml., with 0.1 mg. per 100 ml. in the direct-reacting fraction. The cephalin flocculation test was negative, and the thymol turbidity was 2.0 units.

Samples of sweat were collected from the patient, as well as all other members of his family,

TABLE 1.—*Pulmonary Function Studies and Arterial Blood Studies*

	Predicted Normal	Patient	% *
Pulmonary function studies			
I. Lung volumes			
Vital capacity, ml.	4,250	3,800	89
Residual volume, ml.	1,060	2,300	217
Total lung capacity, ml.	5,310	6,100	115
II. Ventilation			
Minute volume, l/min.	4-6	11.2	
Single breath N_2 test, N_2	<1.5	7.4	
Seven-minute washout, % N_2	<2.5	2.2	
Dead space, physiologic, ml.	150-200	337	
III. Mechanical function			
Maximal breathing capacity, l/min.	131	64	49
Maximal expiratory flow rate, l/min.	400-600	110	
Maximal inspiratory flow rate, l/min.	400-600	125	
IV. Diffusing capacity			
Single breath CO test, ml/min/mm. Hg.	20-40	19	
Arterial blood studies			
	Normal	**Air**	**100% O_2**
Oxygen content, vol. %	18-21	16.77	19.15
Oxygen capacity, vol. %	19-22	16.81	17.23
Oxygen saturation, %	96-99	99.7	100+1.92 †
P_{CO_2}, mm. Hg.	38-42	45	43
pH	7.38-7.40	7.33	7.35

* Per cent of predicted value based on physical characteristics and age.

† Value following + sign refers to milliliters of O_2 per 100 ml. of blood in excess of that required to saturate hemoglobin (i. e., dissolved O_2); normal value for dissolved O_2 is 2.00 ml.

with use of the method devised by Schwartz[9] (Table 2). Concentration of chloride in sweat obtained from this patient was 98, 105, and 122 mEq. per liter on three different occasions. These values are significantly elevated above the upper limit of normal, 70 mEq. per liter, obtained in a series of adults and children studied by one of us (R. F.).

Roentgenograms of the parents' chests were negative.

Course.—On the basis of this information the diagnosis was made of cystic fibrosis of the pancreas. The patient was treated with erythromycin for one week and potassium iodide by mouth for one month. He was also given a therapeutic trial with a pancreatic extract. After one month the patient reported only mild improvement in his pulmonary symptoms. He was changed to a course of prophylactic therapy with sulfadiazine. The patient could not use the pancreatic extract because of the expense. Though it did decrease the number of stools somewhat it did not reduce his appetite significantly. He is at present hunting for a job and will continue under observation.

TABLE 2.—*Concentration of Chloride in Sweat*

Family	Sex	Age, Yr.	Cl, mEq/L.
Patient	M	18	98, 105, 122 *
Parents	M	49	72
	F	47	44
Siblings			
1	M	14	36
2	M	16	34
3	F	20	34
4	M	23	39

* Represents three separate determinations.

Comment

The clinical features in this young man differ from those of the usual patient in that there had been less difficulty with poor weight gain and other evidences of growth failure in the early years. He had less difficulty with pulmonary insufficiency than most patients who have this disease. It should be noted, however, that symptoms suggestive of cystic fibrosis of the pancreas date back to early childhood.

Evidence for most of the diagnostic criteria for this disease exists in this patient despite the fact that an assay of duodenal fluid for proteolytic enzymes was not possible. The history was suggestive of both pulmonary and pancreatic insufficiency. No symptoms were reported that would suggest excessive salt loss. The family history does not give conclusive evidence of involvement of other siblings, though the information is compatible with the possibility that the two children who died had complications due to cystic fibrosis of the pancreas. The history and physical findings, the abnormalities in the roentgenograms of the chest, the evidence for malabsorption in the radioactive olein test and in the vitamin A tolerance curve, and the abnormal excretion of electrolytes in sweat all point to cystic fibrosis of the pancreas. No other condition except adrenal insufficiency is known to cause such a marked elevation of the concentration of electrolytes in sweat. In this

patient there is no evidence of tuberculosis, nor is there any clinical evidence suggesting adrenal insufficiency.

Though the pulmonary infection in children with cystic fibrosis of the pancreas is characteristically an indolent process which causes little systemic reaction, progressive diffuse peribronchiolar inflammation and fibrosis with obstructive atelectasis and focal emphysema are almost constant features which lead to increasing pulmonary insufficiency and eventual death. In this patient, despite the fact that he has not had consistent antibiotic treatment, the relatively minor degree of pulmonary emphysema, infiltration, and focal atelectasis merely restricts strenuous activities. The clinical result in many patients with this disease of present regimens of antibiotic treatment is not as good as the state of this patient who has had little treatment. This suggests that there is considerable variation in the severity of the pulmonary process in different patients. There is also a suggestion in a recent report [2] that in children over the age of 10 years there is less difficulty with progression of the pulmonary disease.

For many years this child was considered to have asthma because of the wheezing character of his respirations. A recent report [7] emphasizes that many children with this disease may have bronchial constriction producing wheezing respirations. This may result from a combination of bronchial spasm, edema, and encroachment on the lumen by accumulated tenacious mucus. In patients with persistent symptoms suggesting asthma or bronchitis, the possibility of cystic fibrosis of the pancreas should be considered.

The abnormality in sweat in this patient was of crucial importance in diagnosing his condition. About 10% of patients with cystic fibrosis of the pancreas do not have complete pancreatic insufficiency.[5,6] In such patients the abnormality in sweat may be the only conclusive evidence of this disease. The malabsorption syndrome in this patient, in all likelihood, is due to some degree of pancreatic insufficiency. The simplicity and diagnostic accuracy of the sweat test make it valuable as a screening test in patients showing a malabsorption syndrome or chronic pulmonary disease with obstructive emphysema and in patients with portal hypertension of unknown etiology. In the older child the single commonest cause of portal hypertension and hypersplenism with biliary cirrhosis is cystic fibrosis of the pancreas.[8] So far, no adult patients with portal hypertension and cystic fibrosis of the pancreas have been reported. In this patient there is no evidence of biliary cirrhosis.

Reports in the pediatric journals have described several patients in whom either the pulmonary disease or the pancreatic disease is minimal or absent.[5,6] Experience with large series of patients in whom the diagnosis of cystic fibrosis of the pancreas was established by pancreatic insufficiency and severe pulmonary disease shows that more than 99% have an abnormal concentration of electrolytes in sweat.[1] This demonstrates the usefulness of this test in screening patients with symptoms suggesting cystic fibrosis of the pancreas. This patient is reported in order to emphasize the fact that cystic fibrosis of the pancreas can no longer be considered only a pediatric problem.

Summary

We describe the case of a boy 18 years of age in whom cystic fibrosis of the pancreas was diagnosed on the basis of abnormalities in the concentration of electrolytes in the sweat, changes in the roentgenograms of the chest, and evidence of malabsorption. The rarity with which a patient with this disease reaches this age is noted, and the usefulness of the sweat tests in the evaluation of adults and children with symptoms suggestive of this disease is emphasized.

Dr. George Bedell assisted in the pulmonary function studies, and Dr. Arthur W. Horsley performed the radioactive fat-absorption studies.

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Recognition and Treatment of Hemopericardium and Hemorrhagic Pericarditis by Pericardiotomy

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The recognition of hemopericardium occurring during the course of acute myocardial infarction when recognized and treated appropriately can significantly change the course of the patient. The differentiation between hemopericardium and hemorrhagic pericarditis may on occasions be extremely difficult. Whether the use of anticoagulants in the treatment of myocardial infarction has increased the incidence of hemopericardium and hemorrhagic pericarditis remains a moot question. However, reports by Leedham and Orbison,[1] Nichol,[2] and Rose, Ott, and Maier[3] have served to emphasize the importance of recognizing the presence of hemopericardium in a patient to whom anticoagulants have been administered.

The report of Laszlo[4] has focused our attention on another aspect of hemopericardium, namely, as to whether constriction of the pericardium can occur as a complication. His report is rather convincing in this respect.

It is the purpose of this presentation to report the clinical course of two patients suffering from acute myocardial infarction, both treated with anticoagulants; the first, representing acute hemopericardium with tamponade, and the other, hemorrhagic pericarditis with clinical behavior similar to that of hemopericardium with tamponade.

Case Histories

CASE 1.—A 44-year-old white man experienced severe squeezing anterior chest pain radiating to the left arm and down to the left hand. Emergency treatment was rendered at another hospital with meperidine and he was sent home. However, his pain persisted, and he complained of nausea, fatigue, and listlessness. When seen by his own physician a few hours after initial symptoms, the electrocardiogram revealed anterior wall infarction, and the patient was transferred to this hospital. Of interest also was a documented history of ileitis, treated medically, and in remission at the time of this incident. On admission to this hospital, he was pale, nauseated, and apprehensive. Blood pressure on admission was 138/80. Examination of the head and neck revealed nothing of interest. The chest was clear, expansions were good, and no rales were heard. Examination of the heart revealed the rhythm to be regular and the P. M. I. in the fifth intercostal space just to the left of the midclavicular line. No thrills, rubs, or murmurs were noted, and the sounds were of fair quality. The abdomen was soft and no viscera were palpable, and there were no areas of tenderness. Peripheral pulses were intact, and there was no evidence for venous disease of the lower extremities. Peripheral edema was not present. Laboratory data on admission revealed normal urine, an elevated sedimentation rate, and a moderately elevated white count. The patient received repository heparin during the first three days of his hospital admission, and bishydroxycoumarin in quantities sufficient to raise his prothrombin time level to twice that of the control level by the third hospital day. Thereafter, bishydroxycoumarin was administered in amounts sufficient to maintain the prothrombin time at a level of 30-40 seconds, control values averaging 15 seconds. On the day after admission, a loud friction rub was heard in the third left anterior interspace and persisted for three days. While chest pain was ameliorated on the day of admission due to analgesics and the administration of oxygen, there was recurrence of severe chest pain on the morning after admission. It was noted at this time that the patient's temperature was 101 F, his pulse rate 96 per minute and regular, and his blood pressure maintained at a level of 140/80. An electrocardiogram recorded on the day of admission was consistent with extensive anterior

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wall myocardial infarction (Fig. 1). The patient's course was uneventful until the fifth hospital day when his temperature was found to be 101 F. He was noted to be tachypneic and raising blood-tinged sputum with coughing. At this time, his prothrombin level was 40 seconds with a control of 15 seconds. Pertinent physical signs were absent in the chest and since pulmonary infarction was suspected, a chest x-ray was recorded at the bedside. This was reported to reveal patchy densities in the left lower lung field and some prominence of the left ventricle. Evidence for thrombophlebitis of the lower extremities was not found at the time. As a prophylactic measure, procaine penicillin was administered, and the patient was encouraged to move freely in bed. Because a prothrombin level of 50 seconds had been reached on the sixth hospital day, the administration of bishydroxycoumarin was temporarily discontinued. By the seventh hospital day, the patient felt very well, his blood pressure and pulse rate were stable, and he was still febrile, his temperature averaging 101.5. On the 8th, 9th and 10th days, he was still raising blood-tinged sputum and on the 9th and 10th days the prothrombin level had stabilized at twice the control level. Administration of bishydroxycoumarin was reinstituted on the 11th hospital day. It was noted on this day that the patient was still febrile, although no further hemoptysis had occurred, but by the 15th day fever had subsided. His course was uneventful until the 20th hospital day when his temperature again rose to 101 F with some dry cough present. On examination of the chest, dullness was present at the left base posteriorly with an occasional crepitant rale, and further pulmonary embolization was suspected. With bishydroxycoumarin therapy his prothrombin level had averaged at least twice control level. On the 22d hospital day, a systolic murmur was heard for the first time at the apex.

Because of a complaint of chest pain on the 24th hospital day, one of several electrocardiograms was again recorded. It revealed the normal evolution of extensive anterior wall infarction with little evidence for extension or reinfarction. Because of the patient's continued febrile course, there was speculation as to whether pulmonary infarction or myocardial infarction was the etiological factor. On the 28th hospital day, despite low-grade fever, partial ambulation of the patient was begun. By the 30th hospital day, he was afebrile, the lungs were clear, there was no evidence of heart failure, and the heart tones were of fair quality. Anticoagulant therapy was discontinued on the 30th day after admission, and the patient discharged to continue his convalescence at home. It was noted that serial electrocardiograms (Fig. 1) had revealed little reconstitution in this 30-day interval, and that the sedimentation rate remained elevated.

The patient was readmitted to the hospital 32 days after discharge. His interim history indicated that he had received digitalis because of dyspnea and basal rales. He was reported to have been afebrile for the first week of his convalescence at home and thereafter to have exhibited a rise in temperature at night. He occasionally complained of transitory precordial pain. Five days prior to readmission, he experienced severe upper left chest pain radiating to the left shoulder and his temperature at this time was noted to be 100 F. There was no cough, diapharesis, or change in blood pressure. On examination, dullness at the base of the left lung again was present. X-ray of the patient's chest on this occasion (Fig. 3) exhibited marked enlargement of the cardiac silhouette and left pleural effusion, and he was admitted again for reevaluation.

It was noted on readmission that he was not cyanotic but was dyspneic on minimal physical exertion. Neck veins were moderately distended and filled from below. The lungs were clear except for dullness at the left base. His blood pressure was recorded at 120/60 and the heart tones were somewhat distant but easily audible. A faint systolic murmur was heard at the apex. The liver edge was palpable, but peripheral edema was absent. No evidence for thrombophlebitis of the lower extremities was elicited. An electrocardiogram recorded on the 1st day of his readmission (Fig. 1) was similar to his discharge electrocardiogram except for diminution of potential in all leads. His venous pressure was 13 cm. of water and on pressure over the liver area rose to 17 cm. of water. His sedimentation rate was 65 mm. per hour. The patient's course on this admission was characterized by a low-grade rise in temperature. It was noted by a consultant that the cardiac silhouette (Fig. 3) was suggestive of pericardial effusion, and that there had been a significant drop in hemoglobin concentration when the value was compared with that obtained on his previous admission. Because of the old history of ileitis, his stools were investigated for occult blood and proved to be negative. Venous pressures repeated on the 3d day of readmission revealed a pressure of 14 cm. of water with a prompt rise on pressure over the liver area and fall when the pressure was released.

On the 5th day of readmission, fever subsided, but signs of consolidation at the left base persisted. Fearing that the patient had again suffered pulmonary embolization, anticoagulant therapy was reinstituted. Fluoroscopy of the patient's chest on this day revealed absent pulsations of the cardiac silhouette and confirmed the pleural effusion at

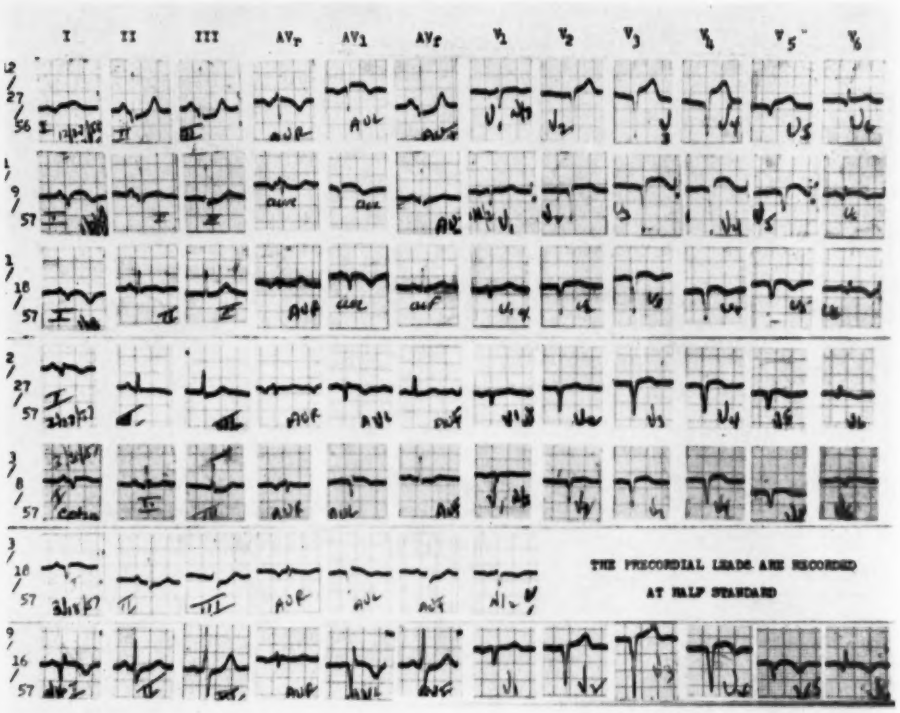


Fig. 1 (Case 1).—Serial electrocardiograms of both admissions. The electrocardiogram recorded on Feb. 27, 1957 is the first one of a series during his second admission. Note small but definite increase in potential of QRS after pericardiotomy (March 18, 1957). This phenomenon was immediately noted on the cardioscope upon release of the percardial tamponade. Six months later (Sept. 16, 1957), except for increased voltage, the configuration is unchanged.

the left base. Thoracentesis on the 8th day after readmission yielded 300 cc. of clear, straw-colored fluid having a protein content of 2%, and bacteriologically sterile on culture. After consultation, the attending physician was persuaded that pericardiotomy was indicated, and on the 10th day of readmission, a surgical consultant elected to relieve the pericardial effusion by needle paracentesis, and 250 cc. of dark fluid was obtained, having a protein content of 5%. The surgeon felt reasonably certain that he had entered the pericardial sac and that this was the source of the fluid, rather than the pleural space. Neither the appearance of the cardiac silhouette nor the potential of the electrocardiogram was altered by the procedure.

Because of progressive deterioration in the patient's condition, pericardiotomy was performed under general anesthesia on the 15th day of readmission without incident. Approximately 1,500 cc. of frankly bloody fluid was slowly aspirated from the patient's pericardial sac, and a large pericardial window was removed by the surgeon in an otherwise uneventful procedure. At the time of operation, a small hemorrhagic ventricular aneurysm was noted on the anterior surface of the left ventricle. The patient's course after pericardiotomy was uneventful. It was noted that the low voltage electrocardiogram obtained prior to pericardiotomy changed significantly immediately after release of the effusion (Fig. 1). The patient was discharged fourteen days after his readmission.

Case 2.—A 48-year-old white man, a laborer, was on his way to work when admitted to the hospital because of the sudden onset of vise-like retrosternal pain which had its onset about one-half hour before admission. He described the pain as radiating to both shoulders, associated with weakness, moderate shortness of breath, and nausea. On the day prior to admission he had a similar episode of lesser intensity, lasting one and one-half hours. In 1943, while in military service and traveling on a train he had an episode of moderately severe precordial pain which lasted about two hours, subsiding spontaneously without further manifestations. He received no medical

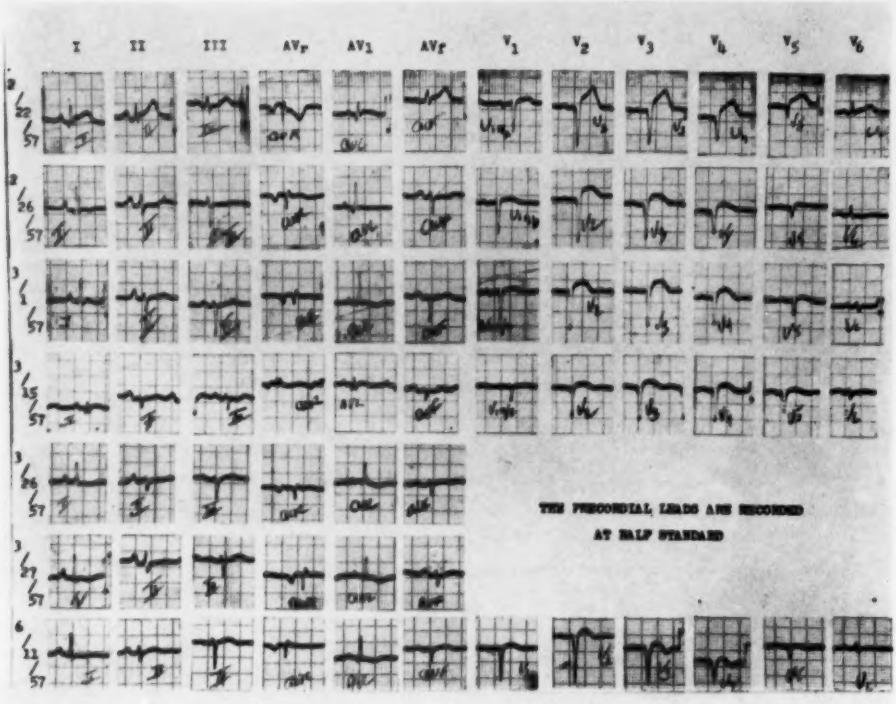


Fig. 2 (Case 2).—Serial electrocardiograms from admission on Feb. 22, 1957 to follow-up examination on June 11, 1957, approximately three months after pericardiotomy. Note significant drop in QRS potential from March 1, 1957, to March 15, 1957, and increase on March 26, 1957, immediately after pericardiotomy. The configuration of the electrocardiogram one year after operation is similar to that recorded on June 11, 1957.

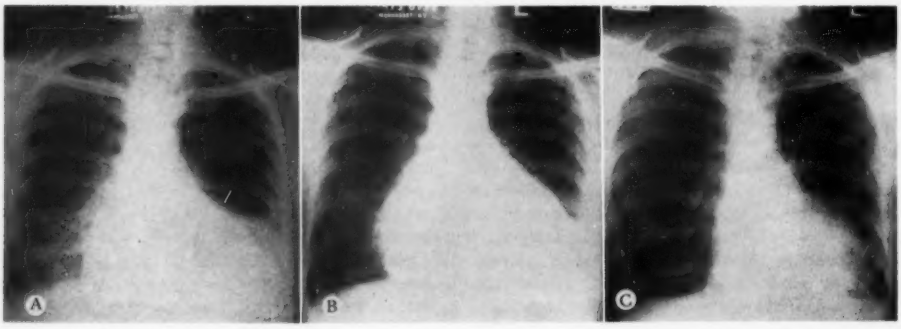
care during that period. The patient also admitted that for a three- or four-month period prior to admission to this hospital he noticed mild constricting chest pain on exposure to cold weather. There was no history of diabetes or hypertension.

On admission, his temperature was 101 F, and he complained of transverse chest pain on deep inspiration and shortness of breath. The neck veins were not engorged, but examination of the chest revealed rales at both bases. On examina-

Fig. 3 (Case 1).—*A*, cardiac configuration just prior to discharge on the first admission. When compared with previous available chest x-rays the change in the cardiac silhouette should have aroused suspicion.

B, appearance of cardiac silhouette the day of second admission to hospital.

C, appearance of chest x-ray six months after pericardiotomy.



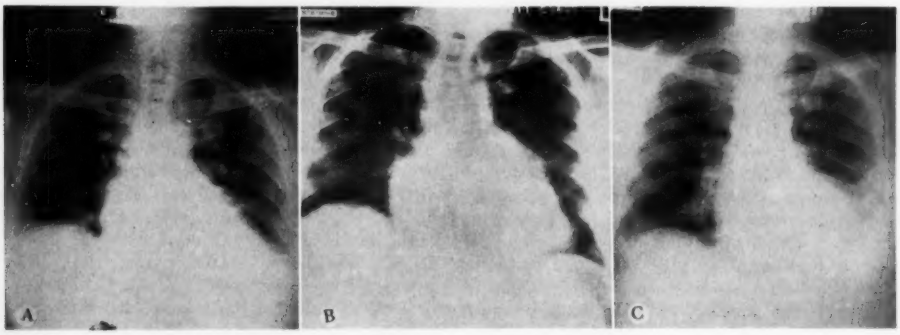


Fig. 4 (Case 2).—*A*, appearance of cardiac silhouette on portable chest x-ray 18 days prior to pericardiotomy.
B, appearance of cardiac silhouette on conventional, overexposed, chest x-ray, 12 days prior to pericardiotomy.
C, follow-up conventional x-ray of chest 34 days after pericardiotomy. On review one year later, the cardia configuration has not changed.

tion of the cardiovascular system, the point of maximal cardiac impulse was in the fifth intercostal space, to the left of the midclavicular line. The pulse and ventricular rates were 96 beats per minute, and the blood pressure 118/76. Cardiac sounds were of fair quality. A short, harsh, systolic murmur was heard at the base, and P_2 was equal in intensity to A_2. The abdomen was not unusual except for mild obesity. There was no edema or evidence of venous disease of the extremities. Laboratory data on admission revealed normal urine, moderately elevated white count, and a greatly elevated serum transaminase. The sedimentation rate was moderately elevated. An electrocardiogram recorded on admission (Fig. 2) was consistent with extensive anterior wall myocardial infarction.

Course.—Despite admonitions concerning complete bed rest, the patient continued to leave his bed, particularly at night, although oxygen was administered by means of an oxygen tent for the first two days. Two days after admission the patient was comfortable, his temperature was 100.2 F, and his lungs were clear except for rales present at the right base. Heart tones were fair, and no friction rub had been heard. Cardiac rhythm was regular, and the blood pressure was maintained at the admission level. At this time the patient was more cooperative and reconciled to bed rest. On the third day after admission, the patient had an abrupt change in course, characterized by a rise in his pulse rate to 110 beats per minute, and a drop in blood pressure to 94/60. He was nauseated, and his color appeared to be slate-gray with slight cyanosis. Examination of the lungs revealed extensive rales, and the quality of the heart sounds had deteriorated. For the first time, a distinct friction rub was heard at the 3d and 4th left interspaces near the sternal border. Because of the appearance of extensive rales in the chest, a mercurial diuretic was administered and cautious digitalization started. The patient's condition continued to deteriorate, and a few hours later he became cyanotic despite oxygen administration, and the heart tones were reduced to poor quality. By the 4th hospital day, the patient's condition had improved, his friction rub had disappeared, and he was resting comfortably in an oxygen tent. His blood pressure had stabilized at 96/68. As a result of mercurial diuretics and digitalization, signs of congestive failure had disappeared. However, he still remained febrile. The patient's condition remained static for the next few days, and on the sixth hospital day he again refused to stay in bed, despite the fact that he was febrile. Anticoagulant therapy, which had been instituted with aqueous heparin on admission, was continued with sufficient bishydroxycoumarin thereafter to maintain a prothrombin level at least twice that of the control value. By the 10th day after admission the patient was completely asymptomatic and without signs of congestive failure. He was more cooperative, but some concern was expressed over his continued mild febrile course. On the 12th day the patient was completely re-evaluated for sources of fever other than his myocardial infarction. No source for thrombo-embolic phenomena could be found. Examination of stools, determination of febrile agglutination values, blood cultures, bedside chest x-ray, and complete blood and urine studies failed to reveal possible sources for his febrile course. On the 13th day of his course the patient was afebrile and comfortable. On the 15th day he was noted again to have fever, and on the 16th day it was noted that his temperature had reached a level of 102 F but he offered no specific complaints. Repeat transaminase determi-

nations failed to reveal values consistent with new infarction. Bedside chest x-ray on the 16th hospital day indicated patchy densities over the right lower lobe, which were interpreted as consistent with pneumonitis, resolving heart failure, or possibly pulmonary infarcts. On the 22d hospital day the patient complained of nausea, had an episode of vomiting, and then complained of epigastric distress. Although digitalis had been administered daily from the third day after admission, it was not felt that nausea and epigastric distress represented digitalis toxicity. His pulse rate at this time was noted to range from 120 to 130 beats per minute, and the blood pressure was again lowered with a value of 94/60. There was a paucity of physical signs, despite the fact that his color was poor, and he obviously appeared in distress. His venous pressure was now recorded at 14 cm. of water, although there were no signs of heart failure. The cardiac findings were unchanged except for the appearance of transitory gallop rhythm. Upon re-x-ray of the chest (Fig. 4) at this time, marked cardiac enlargement with a bulge of the anterior left border was seen. The configuration of the cardiac silhouette raised considerable speculation, and the question of ventricular aneurysm and of pericardial effusion was raised. Throughout his course, the patient's electrocardiogram had not changed materially, except for a significant drop in potential (Fig. 2). On the 23d day of admission the patient's condition had deteriorated. He complained of continuous nausea and retching. His color was poor. There was slight bulging of the neck veins now, and his pulse rate consistently averaged 120 beats per minute. His blood pressure, which prior to this point had been well stabilized at a level of approximately 104/60, now reached values of 80/60. It was also noted that low-grade fever had persisted. His venous pressure at this time was recorded at 18 cm. of water. Re-x-ray of the chest (Fig. 4) again revealed an abnormal cardiac silhouette. Since the possibility of hemopericardium with tamponade had to be seriously considered, anticoagulant therapy was discontinued, and vitamin K_1 oxide was administered. The patient's condition deteriorated rapidly, and he became semicomatose, with gallop rhythm, and paradoxical pulse noted. An electrocardiogram recorded at this time again confirmed definite lowering of QRS potential (Fig. 2). Repeat laboratory determinations of the hemoglobin and hematocrit values now indicated a significant decrease in these values.

Since hemopericardium with tamponade was suspected, immediate pericardiotomy was advised. However, because of the patient's poor general condition the surgical consultant elected to aspirate the pericardium from a subxiphoid approach, withdrawing 90 cc. of fluid blood which clotted readily in a test tube. There was little change in the patient's condition following this procedure. A transfusion of 500 cc. of whole blood was administered, as well as sufficient fluids to effect hydration. Digitalis administration was continued. A second attempt to complete the aspiration of the pericardial sac was attempted about 30 minutes after the first, but this proved to be unsuccessful due to plugging of the needle by clots. Pericardiotomy was then instituted with the use of general anesthesia. Many large clots were evacuated from the pericardial sac, as well as a small quantity of fluid blood. A large area of myocardial necrosis was noted on the anterior surface of the left ventricle and many fibrinous adhesions were separated posteriorly, some of which appeared to be undergoing organization. The patient's postoperative course was uneventful, and he was afebrile on the second postoperative day. His blood pressure was stable at a level of 106/68, and his benign course thereafter was in marked contrast to that noted prior to the pericardiotomy. The patient has been followed now for more than a year, and he is entirely well, and, contrary to advice, has returned to heavy, manual labor.

Comment

Both patients received anticoagulant therapy with bishydroxycoumarin. Good anticoagulant levels were achieved and maintained with one episode occurring in the course of each patient in which undesirable high levels of prothrombin (50 seconds) were attained. However, the complications noted were not related temporally in either instance to the prothrombin level.

Recurrent fever was a feature of the clinical course of both patients, and myocardial infarction was thought to be the source of the fever. In the first patient, complicating pulmonary embolism despite good anticoagulant levels undoubtedly contributed to his febrile course. Friction rub was heard in both patients early in their courses and recurred shortly before pericardiotomy in the second. An enlarging cardiac silhouette, rising venous pressure, diminished hemoglobin and hematocrit values, lowering of ventricular potentials in electrocardiogram, all served to herald the critical phase in each patient. With reference to the first patient, if the index of suspicion had been high on his first admis-

sion (Fig. 3) the correct evaluation of persitent fever and an enlarging cardiac silhouette on x-ray in the absence of heart failure may have resulted in earlier withdrawal of bishydroxycoumarin.

Cardiac rupture after myocardial infarction is generally thought to occur more frequently in those persons who engaged in vigorous physical activity after the appearance of their initial symptoms. Our first patient was released from one hospital after emergency treatment and advised to return home. This required a circuitous train ride, and he carried a heavy briefcase filled with legal papers. The second patient worked at hard manual labor on the day prior to admission, despite severe chest pain on the preceding day. While neither of our patients sustained cardiac rupture, at pericardiotomy each had evidence of extensive myocardial infarction with localized bulging of the ventricular wall. It may be presumed that seepage of blood through the infarcted muscle was responsible for the presence of hemopericardium in the first patient, and that the anticoagulant regimen may have been contributory.

That there may be some question as to the use of pericardiotomy in these cases is acknowledged. Needle paracentesis of the pericardium inherently carries an appreciable morbidity and mortality rate. With modern anesthesia and a capable thoracic surgeon, morbidity and mortality are negligible after pericardiotomy. In some instances, as in the case described by Rose, Ott, and Maier,[3] the procedure has been successfully executed with the use of local anesthesia. Pericardiotomy does offer the opportunity for direct visualization of the pericardium. Usually, infarcted myocardium can be readily visualized and left undisturbed. Adequate drainage of the pericardium is achieved, and its contents are available for biopsy and bacteriological study.

In both of our cases, organization of the resected pericardium was described by the pathologist. This is important information and has added significance since Laszlo's[4] excellent description of a patient he observed from the time of his initial myocardial infarction, treated with anticoagulants, to the onset of verified hemopericardium, and final decortication and cure for constrictive pericarditis. We believe this patient's course could have been significantly altered if his hemopericardium had been treated by pericardiotomy at the time of recognition, rather than needle paracentesis.

While it has been generally accepted that blood in the pleural space will organize and in some instances necessitate decortication of the lung, there is no general agreement concerning organization of blood in the pericardial sac.

Following trauma to the chest wall, reports by Elkin and Campbell,[5] and Ehrenhaft and Taber[6] have indicated organization and constriction of the pericardium as a result of hemopericardium. In an effort to experimentally delineate this problem, Ehrenhaft and Taber[6] injected autogenous whole blood into the pericardial sacs of dogs and reported organization of the pericardium, with some of the features of constrictive pericarditis. In these experiments, quantities of blood as small as 100 cc. were injected and were sufficient to cause the changes of constrictive pericarditis.

It is not our intention to enter into a controversy as to the results achieved by the use of anticoagulants in patients with myocardial infarction, or as to which patient must receive anticoagulants. These problems have again been adequately reviewed by Wright,[7] and Russek and Zohman.[8] We do wish to emphasize that, despite good laboratory facilities and due diligence exercised by physicians, the use of potent anticoagulant drugs is fraught with some danger for the patient. Bleeding at lower therapeutic levels of anticoagulation has led us to reevaluate the Quick one-stage test to assay prothrombin levels. Preliminary studies by us confirm the work of Ware and Strangell[9] that a more sensitive test such as the Owren test may be a more reliable indicator of prothrombin activity. Its use by more clinical laboratories may help anticipate serious hemorrhagic phe-

nomena, such as hemopericardium. It is doubtful, however, that hemorrhagic pericarditis has any relationship to anticoagulant therapy.

Finally, while the first patient at pericardiotomy demonstrated a large amount of fluid blood in the pericardial sac, the pericardial sac of the second contained only a small amount. Nevertheless, pericardiotomy significantly altered the course of each patient. In the first, the actual mechanical presence of a large volume of fluid in the pericardial sac could have been sufficient to explain the symptoms of tamponade and poor heart function. In the second instance, this explanation is, of course, not tenable. It has been our assumption that a small amount of blood in the pericardial sac, as exhibited by the second patient, either caused difficulty because of the mechanical presence of clots, or it was responsible for initiating a deleterious stress reaction similar to that described by Dressler,[10] as possibly being etiological for the postmyocardial infarction syndrome.

Both patients, observed for more than a year now, have returned to their former occupations and are well. The electrocardiograms and cardiac silhouettes of both strongly suggest the presence of ventricular aneurysm.

Summary

Two patients have been described with acute myocardial infarction. Each was subjected to pericardiotomy as an emergency procedure. In the first patient, it was strongly suspected that the large quantity of blood found in the pericardial sac had collected there from seepage through the infarcted area. The second patient had a small quantity of blood in the sac but many blood clots. In both, there was evidence histologically of organization on the pericardial biopsy specimens. Pericardiotomy dramatically altered the course of each patient.

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Syphilis

Review of the Recent Literature

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(Concluded from page 483)

Prenatal and Congenital Syphilis

Serology in Prenatal and Congenital Syphilis.—Putkonen and his group [117] present an answer to the question, "Is the placenta of a syphilitic mother more readily traversed by the complement-fixing antibody than by the flocculating antibody?" They compared the serologic tests performed on specimens of blood from 211 penicillin-treated mothers with specimens of cord blood from their 213 infants, including two pairs of twins. Of the infants, 25% showed a positive Wassermann test and 37% a positive Kahn test. The difference is reduced when one takes into consideration that the Wassermann test employed was considerably less sensitive than the Kahn test. On the basis of their results, they conclude that both antibody reagins traverse the placenta equally readily. Further, they feel that in the studies performed elsewhere showing a predominance of the positive complement-fixation test over the positive flocculation reaction in the infants, the former test has probably been more sensitive than the latter.

Lighter [118] stresses the fact that syphilis in pregnancy is doubly important because it affects the life and welfare of both mother and baby. He defines the criteria for serologic problem cases and recommends the TPI test as an excellent method of differentiating between syphilis and a biologically false-positive standard serologic test for syphilis. The inclusion of pregnancy as a cause of a biologically false-positive reaction is an assumption. His analysis of 100 serologic problems included 28 pregnant patients.

Results of the First Thousand Routine Serological Tests for Syphilis Carried Out on Mothers and Children in Seville.—Morales and his group [119] point out that the results of serological tests for syphilis carried out in the Central Serological Laboratory, Seville, since 1956, have revealed an incidence of unsuspected syphilis in Spain higher than that in other countries in Europe or of America.

Höfig [120] reported the case of an apparently adequately treated and seronegative mother giving birth to a child who showed signs of congenital syphilis. The woman underwent several courses of antisyphilitic treatment with massive doses of penicillin supplemented by bismuth and neoarsphenamine. At the end of this therapy all serum tests were nonreactive. After having become pregnant, she underwent further "prophylactic" treatment with nine million units of penicillin during the third to fourth month of pregnancy. Despite the fact that she remained seronon reactive throughout the whole period of gestation, a foetus

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sanguinolentis born at full term showed signs of congenital syphilis (osteochondritis).

Effects of Untreated Syphilis on the Obstetric History and Progeny of the Human Woman.—In a study of the offspring of untreated syphilitic women, Bonugli [121] analyzed the obstetrical and medical history of 445 parous women and determined the outcome of conception in 324 of these. All pregnancies which had been preceded by any antisyphilitic treatment were discarded. Bonugli concluded that the chance of miscarriage or stillbirth interrupting a conception is about 25% and death within one year after birth about 38%. Thirty-five to 66% of the offspring examined were found to be syphilitic. It is unfortunate that comparison could not be made with the results of pregnancy in the same geographic area in nonsyphilitic women.

Venereal Diseases in the Newborn.—Recent progress in congenital syphilis, false-positive serum reactions and gonorrhea are discussed by Willcox [122] in connection with the newborn. The use of penicillin in pregnant women has reduced the incidence of congenital syphilis to the point of possibly complete eradication in many countries in the future. Case-finding through routine serum testing of the expectant mother and the new rapid treatment with penicillin are the essence of this progress. As false-positive serum reactions increase in relative proportions to the truly positive ones, they are of increasing concern. The treponemal-immobilization test, the treponemal-agglutination test, and the more recent treponemal-complement-fixation test have proved useful in establishing false-positive reactions; and as antigen for the latter test becomes more available, it is hoped its use will become widespread throughout England. Progress has also been made in the prevention of ophthalmia neonatorum; however, gonorrhea is far from being under control. The position in this connection appears to have become stationary. Willcox urges that prophylactic treatment be continued and that the present progress be consolidated by continued use of existing methods of control.

Hemorrhage of Syphilitic Origin in the Newborn.—The *Archives of Pediatrics* [123] reprinted a presentation by Wilson in this same journal in 1905 (22:43-51). This paper was read before the Philadelphia Pediatric Society in Dec. 1904, by the author, who was then Visiting Physician to the Philadelphia Lying-in-Charity Hospital. Syphilitic purpura is discussed, and it is noted that in such cases syphilis itself is probably not the primary cause of the hemorrhage. More likely, it is the constitutional effects of syphilis underlying the degenerative changes in the blood and vessels which cause the hemorrhage. Evidence of infection in the mother is often obscure and may be entirely lacking since the infection may be transmitted directly from the father. Ten cases are cited, noting the course of events, clinical manifestations, and their relationship to the histories. In diagnosis, the author states that hemorrhage appears usually in children in whom the characteristic signs of syphilis are not present.

Skeletal Lesions of Infantile Syphilis.—Mukherji [124] presents a case of infantile congenital syphilis with skeletal manifestations. Other than the reactive serologic test for syphilis, the clinical and radiological evidence of involvement of the skeletal system was the only manifestation of the disease.

Congenital Syphilis as a Cause of Mental Deficiency.—Courville [125] described a patient with mental deficiency, as well as cerebral palsy, apparently due to congenital syphilis. He points out that in the past congenital syphilis played a significant role in the production of mental deficiency. The incidence averaged approximately 6% in the period ending about 1935. In the past 20 years, it has dropped to about 4% It is to be anticipated that in the future syphilis will play a decreasing role in the causation of mental deficiency, thanks to the efficiency of antibiotic therapy. The pathological changes found in the central nervous system in those who die in child-

hood or early adolescence are syphilitic meningitis, syphilitc vascular disease (including endarteritis), or congenital paresis. In those who die after the age of 16 years, chronic meningovascular syphilis is more likely to be present, the chronic meningeal or meningovascular form being less likely to bring about a fatal issue.

Interstitial Keratitis.—Three cases are presented by Oksala [126] which show the difficulties encountered in the treatment and recurrence of interstitial keratitis. Results in other cases are also discussed, including some 16 cases (25 eyes) of the disease associated with congenital syphilis treated with local cortisone or hydrocortisone. Recurrences among 8 of these 16 necessitated treatment of several months' duration. It is considered that corneal neovascularization clearly reduced recurrences only where there was involvement of the main part of the cornea. Besides this, atrophy and formulations of scars in the iris, the ciliary body and the chamber angle also had the effect of inhibiting recurrences. Local hydrocortisone only has been used with results equal to those obtained with combined mydriatic and hydrocortisone therapy. Benefits of this treatment are less frequent occurrence of goniosynechias, and increased working ability of the patient during prolonged treatment (due to omission of mydriatics). A theory as to later recurrences will require several years of observation. Oksala concluded that the treatment of interstitial keratitis associated with congenital syphilis is not fully solved. These observations were made by the ophthalmic department of the Central Finland Regional Hospital.

Oksala [127] directed attention to the significance of chamber angle changes reported in pathoanatomic studies and biomicroscopic observations. An eight-year-old girl had interstitial keratitis associated with the active stage of congenital syphilis, treated at the Central Finland Regional Hospital. One eye was diseased with trabecular synechias and increased pigmentation visible. During the course of the disease hyperemia of the iris first disappeared from the pupillary and much later from the ciliary part. The other eye, clinically asymptomatic, "showed in its chamber angle abundant trabecular synechias, increased pigmentation, and two blood vessels which emerged from the ciliary body and having passed over the trabecular sclera ran for a short distance within the cornea." Oksala concludes that iridocyclites, occurring either in fetal or early neonatal life, may be contributory in the genesis of interstitial keratitis, and that the formation of trabecular synechias may promote the onset and later recurrences of interstitial keratitis.

MacFarlane [128] reports on a congenital syphilitic, 44 years of age, who, while under treatment for interstitial keratitis, developed a severe posterior uveitis which progressed to blindness, despite systemic penicillin treatment and local and systemic steroid therapy. MacFarlane emphasizes that, while local cortisone therapy may produce a complete remission of signs in the anterior segment of the eye in interstitial keratitis, it is ineffective against inflammation of the posterior segment.

Cogan's Syndrome.—Combination of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms associated with vertigo, nystagmus, tinnitus, and usually complete deafness, is referred to as Cogan's syndrome. This syndrome is first noticeable with the bilateral appearance of a patchy, granular type of infiltrate situated predominantly in the posterior half of the cornea, which becomes vascularized later in the course of the disease. Auditory symptoms may precede, but usually follow, the ocular symptoms. Mild leukocytosis and occasional eosinophilia are the only indications of a systemic disease, supposed to be intimately associated with Cogan's syndrome, the origin of which was heretofore believed to be allergic, infectious, or vasomotor in nature. Two of the three patients reported by Crawford [129] developed systemic polyarteritis nodosa; the third patient showed signs of a systemic disease of the collagen variety. These findings lend credence to

the idea that Cogan's syndrome is an early localized manifestation of polyarteritis nodosa capable of an acute fatal or chronic course. Eisenstein and Taubenhaus [130] made observations on three cases of Cogan's syndrome associated with cardiovascular disease; in two, aortic insufficiency due to a valvulitis developed after the onset of the eye-and-ear symptom complex, and in one, necrotizing angiitis subsequently developed.

Cardiovascular Syphilis

Congenital Syphilitic Cardiovascular Disease.—Pei, Shan, Chiu, and Wang [131] discuss the literature on cardiovascular involvement in congenital syphilis. They observed a case in a 14-year-old boy who died shortly after admission to the hospital.

Cardiovascular Syphilis in Neurosyphilitic Patients.—In a group of 204 patients (127 men and 77 women) treated for neurosyphilis, Raaschou-Nielsen and Kopp [132] demonstrated cardiovascular syphilis in 20%. Complicated types of aortitis occurred in 8.4%, uncomplicated in 11.7%. Among patients with syphilitic aortitis, men were in the majority and more so in complicated than in uncomplicated cases. Among the dead patients who before or after death were found to suffer from cardiovascular syphilis, a greater number of men than of women died with their disease as a primary cause of death. Complicated syphilitic aortitis was noted with the same frequency among the neurosyphilitic patients of this study as in the literature concerning nonselected late syphilitic patients.

Correlation of Anatomic and Roentgen Changes in Arteriosclerosis and Syphilis of the Ascending Aorta.—The radiological changes in syphilitic aortitis and arteriosclerosis were studied by Lodwick and his group [133] in 72 aortas obtained at necropsy at the Veterans Administration Hospital, Iowa City. The commonly-held view that intimal calcification in the ascending aorta is usually due to syphilis was substantiated. Calcification does occur in the ascending aorta in atheroma, principally around the ostia of the coronary arteries and great vessels and on the posteromedial wall. In syphilis the ascending aorta is more uniformly affected and the pattern is one of numerous small flaky plaques, entirely different from the large, dense, isolated plaques of atheroma. A method of measuring the length and width of the aortic shadow on the posteroanterior chest radiograph is described, the two measurements added together being termed the aortic index. Use of this index takes into account the dilatation and elongation which occurs in syphilis. It was found that, taking both sexes together, 85% of patients with an aortic index over 20 cm. and 100% of those with an index of over 24.2 cm. showed serological evidence of spyhilis.

Aortic Arch Syndrome.—A case of syphilitic mesaortitis with aortic regurgitation and absent pulse in the left arm was recorded by Rajagopalan and Rao.[134] Coarctation was suggested by the fall in blood pressure in the lower limbs and the presence of narrowing of the aorta in the roentgenogram. Autopsy revealed alteration in the arrangement of the great vessels at the arch, obliteration of the left subclavian artery, pseudocoarctation just below the left subclavian attachment, syphilitic mesaortitis, and extensive atheromatosis.

Aneurysm of the Aorta.—Bourne and Gaspar [135] studied 65 cases of aortic aneurysm of which seven were syphilitic in origin. Five of these were of the thoracic and two were of the abdominal aorta. In the entire series, there were 11 deaths due to rupture of the aneurysm. All were arteriosclerotic aneurysms. In general, this study is in agreement with other recent series showing that most aortic aneurysms are due to arteriosclerosis and that more of them involve the abdominal than the thoracic aorta.

According to Roberts, Danielson, and Blakemore [136] between Jan., 1950, and Jan., 1956, 65 patients with abdominal aortic aneurysms were admitted to the Hospital of the University of Pennsylvania. Only

three of them had a positive serologic test for syphilis. During the same time 36 patients were seen with aneurysms of the thoracic aorta. Eighteen of the 36 had a positive test for syphilis. These figures strongly confirm the view of many authors that today the majority of abdominal aneurysms arise on the basis of arteriosclerosis and not syphilis. In comparing the 36 patients with aneurysms of the thoracic aorta, recognition and confirmation is given to the fact that a higher proportion of thoracic aneurysms than abdominal aneurysms arise from syphilitic infection. In this total group of 101 patients having aortic aneurysms, operative and nonoperative groups are compared. If untreated, approximately one-half of the patients with aortic aneurysms died within a year. Excision of aortic aneurysms with restitution of blood flow by grafting, if needed, has improved the prognosis and presumably will become less hazardous as more experience is gained in the procedure.

Complete Heart Block Due to Syphilis.—Two case histories of complete heart block due to syphilis were presented by Weinstein and his group.[137] The first was seen in 1932, and the second patient was examined in 1955. These two patients suffering from the Stokes-Adams syndrome on the basis of gummatous disease of the interventricular septum are added to the 18 reported in the literature. One of these patients, a 37-year-old white woman, was admitted to the hospital with typical heart trouble symptoms. None of her laboratory reports were positive for syphilis. Her husband tested negative, but their only child, a girl, tested positive for syphilis. The woman died in 14 days of gummatous disease. The second case was a 50-year-old Negro man. He suffered for some seven weeks of increasing breathlessness and later vertigo. During an attack of syncope on the street, he was arrested on the charge of intoxication and was later admitted to the hospital. On the 10th day of hospitalization, his third episode ended with death. Postmortem examination revealed a gumma of the right ventricular wall, extending into the interventricular septum. At the present, although syphilis is a disease of historical importance primarily, it can not be overlooked as a cause of illness. Osler's advice, "Know syphilis and you know medicine," still stands.

Atrial Fibrillation in Syphilitic Aortic Insufficiency.—During the years 1950 to 1954 the diagnosis of syphilitic aortic insufficiency was made 125 times at the John Gaston Hospital, Memphis, Tenn. Atrial fibrillation was found by Smith and Stern [138] to be present in 11.2% of these cases. This percentage compares roughly with the incidence of atrial fibrillation in rheumatic fever (14.3%). These workers conclude that the presence or absence of fibrillation can not be used as a differential diagnostic point between syphilitic and rheumatic aortic regurgitation.

Neurosyphilis

Interest in neurosyphilis is tending to take the direction of physiological responses, incidence in general, and in special groups. Csonka [139] reports on an interesting study of sweat response to general body heating in 24 patients with clinical neurosyphilis and in 5 controls. The control subjects gave normal sweating responses. Twenty of the 24 neurosyphilitics showed marked sweating deficiency which was symmetrical in 15 and asymmetrical in 5. In 2 patients with Charcot joint, less sweating was seen over the affected joint than in the corresponding area of the other leg. Four of 14 patients with lightning pains showed normal sweating in the limbs affected, but 10 gave diminished or absent sweating responses in the painful areas.

Durel and Borel [140] observe that the frequency of neurosyphilis has steadily diminished in France, as well as elsewhere. They cite certain observations based on the 1953 study of J. Lereboullet. It is empty to speak of treatment as preventative. It is prudent to treat a patient with abnormalities limited to the cerebrospinal fluid as though he has manifest neurosyphilis. The changes

in the cerebrospinal fluid do not distinguish the various types of nervous system involvement, such as hemiplegia, paralysis of a cranial nerve, etc. Durel and Borel still favor acetarsone. They call attention to the relatively favorable results from penicillin in parenchymatous syphilis, such as paresis and tabes, but the results are less satisfactory in neurovascular involvement and optic and acoustic nerve disease. In these latter conditions only cortisone seems of value in limiting the extension of the process. Durel and Borel point out the difficulties in exact diagnosis, the very limited value of the blood serologic procedures, the inexact significance of the results of lumbar puncture, the development of lesions in the absence of treponemes, and reinfection.

Neurosyphilis in Bantu Men.—According to Woods [141] neurosyphilis in 24 Bantu men admitted to King Edward VIII Hospital, Durban, during 1950, accounted for approximately 0.5% of all male medical admissions and 9.5% of neurological cases. In addition, 21 other patients might have had the disease but failed to meet all the strict criteria enumerated. These cases are discussed briefly in an effort to estimate the incidence rate. It is pointed out that this does not include mentally deranged patients; also it is mentioned that figures for the past two years remain substantially unchanged. It is concluded that tertiary syphilis is a serious social and economic problem (syphilis continues a most prevalent disease among these people), and a plea is made for an energetic campaign to eradicate the disease.

Neurosyphilis Among the Employees of a Railway Company in the Deccan.—Among a total of 79 cases of syphilis diagnosed and treated at the Kurduvadi Hospital of the Barsi Light Railway Company during April, 1948-March, 1952, 11 cases were found by Koeingsfeld [142] to be of the nervous system. All patients were men between 30 and 50 years of age. Because of this high incidence of nerve involvement (13.9%) in a country where neurosyphilis is considered a rare condition, these cases are discussed in detail, including the various clinical manifestations, methods of diagnosis, and treatment. Cases included four with hemiplegia, three with syphilitic meningitis, and four with lesions mainly affecting the peripheral nerves. There is no short cut to permanent cure of syphilis, and if neurosyphilis is to be avoided all antisyphilis treatment should be given in sufficiently large doses.

Tabes Dorsalis with Special Reference to Primary Optic Atrophy.—Hahn,[143] utilizing the thoroughly studied Johns Hopkins Hospital material, presents a scholarly paper on tabes dorsalis and primary optic atrophy. He points out that the pathogenesis of these conditions is unknown. Progression following no treatment, metal chemotherapy, malaria without penicillin, penicillin and malaria, and penicillin without malaria, is compared. It appears that there is no significant difference in degree of loss of vision after treatment by these various modalities, or in relation to the presence or absence of pleocytosis before treatment. The prognosis was better, however, in those with relatively little visual loss at the time of treatment. The prognosis in treated optic atrophy for retention of some vision is relatively good; over a period of seven to eight years of direct observation after therapy, visual acuity had deteriorated to this stage in only 20% of the patients.

Prophylaxis

Durel [144] proposes, among other prophylactic studies and measures to prevent prostitutes from transmitting venereal diseases, that they receive an intramuscular injection of 2,400,000 units of benzathine penicillin monthly. After discussing the objections to this procedure, he concludes that it is safe and effective and advises further study of this problem.

General Therapy

Penicillin is still the standby in the present treatment of syphilis.[145-147] It has an important place in the abortive treatment,[148] and new penicillin preparations are being

investigated. One of them is the new coated benzathine (penicillin G) [tablet] [149] which delays absorption but offers no real advantage over regular penicillin G tablet or phenoxymethyl (penicillin V) tablet.

Cortisone and Syphilis.—During a five-year period, 120 patients with syphilis at various stages were treated by deGraciansky and Grupper [150] with a single course of penicillin, preceded by treatment with cortisone. (*a*) Cortisone prevents or diminishes, in most instances, the clinical Herxheimer reaction and in particular any febrile response. This is found both in recent and long-standing cases. (*b*) Cortisone modifies the clinical picture of syphilis, a variable improvement occurring, depending on the stage and severity: chancre, secondary syphilides, cutaneous and mucous gummata, some subjective sensations of neurological involvement, interstitial keratitis. (*c*) Cortisone significantly reduces the pathological evidence of activity: diminution or disappearance of treponemes; fall in the concentration of reagin in primary and secondary syphilis and in tertiary with clinical manifestations; lessening of cerebrospinal fluid abnormalities. By contrast, in the so-called specific serological tests, there are no alterations in reagin concentration when it is low. (*d*) Cortisone does not diminish sensitivity of Treponema pallidum to penicillin, nor is the usual course of syphilis after penicillin treatment altered. (*e*) Cortisone is a useful ancillary treatment in certain tabetic manifestations (lightning pains and gastric crises) and in interstitial keratitis. (*f*) Further, penicillin is better tolerated by allergic subjects, by pregnant women, and in aortic and neurological syphilitic involvement.

Does Penicillin in Fact Mask Syphilis?—Some 10 to 13 years before this report by Durel and Hardy [151] a number of examples were published of treatment of gonorrhea with low doses of penicillin (100,000 to 200,000 units in aqueous solution). The low doses arrested but did not cure the disease. They were also capable of masking a syphilitic infection, i. e., delaying its appearance in clinical form. At the higher doses of penicillin preparations, such as benzathine penicillin G, such occurrences are rare and many of those reported are disputable. Such a dose of penicillin administered monthly to prostitutes would be an effective prophylactic against both syphilis and gonorrhea. Such measures are considered needed in France now to protect the health of the nation, for while syphilis has declined, gonorrhea remains rampant. Problems connected with the administration of this project are discussed briefly. Pertinent statistical data are included and the literature is reviewed. A trial study of the effectiveness of such long term penicillin prophylaxis in a sample of prostitutes is suggested.

Treatment of Early Syphilis

The therapy of early syphilis is receiving general evaluation in different quarters and with new preparations. Joulia and Texier [152] contribute a personal, effective scheme of penicillin treatment of this phase of syphilis. Willcox and his co-workers [153] compare the effect in 864 cases of primary and secondary syphilis of three different treatment schedules. Of those followed for one year or more, 7.2% of the patients treated with penicillin, arsenic, and bismuth were considered failures. When penicillin and bismuth alone were used, 9.2% were considered failures, and following penicillin alone in higher dosage, 3.6% were failures. The authors believe that the higher dosage of penicillin and the decreased possibility of reinfection due to the smaller amount of infectious syphilis in the community explain the superior effect of penicillin alone. They conclude that penicillin alone is the treatment of choice in early syphilis. Sixty-two patients with primary syphilis and a negative serologic test, 107 with primary syphilis and a positive serologic test, and 137 with secondary syphilis were treated by Bolgert and Levy's [154-156] method. The patients received one intravenous injection of 0.1 gm. of mercury cyanide on three successive days. For the next three days

they were given 1 million Oxford units of penicillin in daily injections of 200,000, 300,000, and 500,000 units dissolved in isotonic sodium chloride solution; each of these doses first was administered in eight and later in five divided doses. For the next 14 days the patients received 500,000 Oxford units of penicillin in the morning and 500,000 units in the evening of each day. The penicillin therapy was discontinued after 17 days when a total dose of 15 million units of the drug had been given. Clinical and serologic examinations were performed every 14 days until the patients had negative reactions to both flocculation- and complement-fixation tests. The examinations were repeated at 3-month, at 4-month, and at 6-month intervals, and finally once a year. Of the 306 patients, 63 were lost to follow-up, but 43 of the 63 had negative reactions to serologic tests for several hundred days. Of the remaining 243 patients whose follow-up examinations were continued for periods up to 113 months, 230 obtained satisfactory results. They were clinically normal and had negative serologic tests. Seventeen of these became reinfected. Thirteen of the 243 patients were therapeutic failures. Of these, two were considered as clinical failures, four were considered as questionable, and seven had positive reactions to serologic tests in the absence of clinical manifestations. All lumbar punctures except in one patient gave normal results. None of the 37 children born to mothers who were given this treatment manifested congenital syphilis. The conclusion seems justified that 94.5% of the results were definitely satisfactory.

Landy, Rein, Thomas and Kelcec [157] report on 24 patients with early infectious syphilis who received 1.2, 2.4, or 4.8 million units of penicillin (procaine penicillin G in oil with 2% aluminum monostearate) in single or multiple sites. These patients were followed from four to eight years, and serological studies were made with the newer treponemal tests, as well as the usual serological tests. Twenty-three of the 24 were found to be normal on clinical examination, and no relapses occurred. One patient, a homosexual, had a new infection (reinfection) four and a half years after the original treatment.

Treatment of Syphilis with Antibiotics other than Penicillin.—Olansky and Garson [158] review the literature and comment on some of the possible choices available to the physician who, for whatever reason, desires to treat a patient with syphilis with an antibiotic other than penicillin. Numerous antibiotics have been demonstrated to be effective antitreponemal agents in animals. Chlortetracycline, chloramphenicol, and possibly oxytetracycline have been successfully used in sufficient numbers of patients with syphilis to demonstrate their effectiveness in early syphilis, benign late cutaneous syphilis, neurosyphilis, and prenatal syphilis. There is little reason to believe that these three drugs would not be effective in adequate dosage in latent syphilis and cardiovascular syphilis. Carbomycin and erythromycin appear to Olansky and Garson to be very promising agents in the treatment of syphilis, but further evaluation is indicated before the authors would willingly recommend their widespread use in the treatment of this disease.

Clinical Trial of Novobiocin Calcium (Cathomycin) in the Treatment of Primary and Secondary Syphilis.—Edelson [159] gave two patients with primary syphilis and one with early secondary lesions novobiocin in doses of 0.5 gm. dissolved in 500 ml. of 5% dextrose, intravenously, twice daily. The only ill side-effect was acute phlebitis in the cubital and arm veins, due to slow administration of the drug when administered for a period of from three and one-half to four hours. The same amount (500 ml.) administered within a two-hour period caused no ill effect. All three patients were considered failures, and novobiocin is not presently recommended in the treatment of syphilis.

Treatment of Primary Syphilis with Synnematin B.—The question of the possible use of synnematin B in the therapy of syphilis was suggested when two cases

of pinta were cleared during synnematin therapy for typhoid in Mexico. Since the causative agents of pinta and syphilis, Treponema carateum and Treponema pallidum, respectively, appear morphologically similar and respond to the same treponemicidal agents, Wheeler et al.[160] felt that there was a reasonable possibility that synnematin might be effective against the spirochete of syphilis. First, they demonstrated a distinct treponemicidal effect for synnematin in both experimental rabbit syphilis and in vitro. Then, a 22-year-old man with a seroreactive darkfield positive penile chancre was treated with an initial intramuscular injection of 1,000,000 units of synnematin B, followed after 24 hours by 40,000 units three times daily for eight days (960,000 units). The course of events after synnematin therapy was found to be similar to that following penicillin treatment in primary syphilis. In view of this similarity and the results of synnematin treatment of experimental syphilis in animals, it is believed that synnematin B may prove to be a valuable injectable drug in the treatment of syphilis in penicillin-sensitive persons.

Treatment of Ocular Syphilis

Interstitial Keratitis After Adequate Penicillin Therapy.—Oksala[161] reports a boy who received two courses of 4.5 million units of penicillin and one course of 6 million units of penicillin within one and one-half years, beginning at the age of two, for congenital syphilis. At the age of 11 a rather mild interstitial keratitis developed which cleared rapidly with local hydrocortisone therapy.

The Modern Treatment of Uveitis.—Correct diagnosis is a prerequisite for successful and rational treatment of uveitis. The ophthalmologist, rather than the internist, should captain the diagnostic team, and it may prove helpful to separate uveitis into granulomatous and nongranulomatous types, if possible. The use of steroids appears to be the treatment of choice, the most promising ones being the newer metesteroids (prednisone and prednisolone). Most failures in administration appear due to use of topical therapy when systemic therapy is required, or inadequate systemic doses. Indications are that fever therapy should be reserved for cases that do not respond to adequate doses of steroids or to those where steroids are definitely contraindicated. Results of a survey by Nielsen and Kirby[162] of 30 outstanding ophthalmologists of the English-speaking world are as follows: Three prefer fever therapy; 4 use both forms of nonspecific therapy (neither preferred); and 23 prefer steroids (14 of these using steroids almost exclusively). Specific therapy is desired when possible. Until this can be carried out in all cases, nonspecific treatment continues important and is discussed at length along with specific therapy including that for syphilitic uveitis, toxoplasmosis, actinomycosis, and other conditions.

Treatment of Late Latent Syphilis

Potassium Iodide Test of Cure in Severe Gummatous Syphilis and Simple Iodide and Bismuth Treatment in Late Latency.—Hoffman[163] calls attention to the use of potassium iodide as a diagnostic and therapeutic aid in the management of syphilis, pointing out that it is of value in two main diagnostic situations: (1) the late latent stage of syphilis in which weakly positive serological reactions are frequently encountered; (2) in the case of patients presenting mucosal, skin, or bone lesions suggestive of gummata, but in whom serological tests are technically not feasible. He recommends giving 5 to 10 ml. 10% potassium iodide three times a day as a therapeutic test of cure, its effect on the existing lesions being observed. (No ill effects have apparently been observed by Hoffman from this rather large dosage.) In the elderly untreated syphilitic who appears to be in equilibrium with his disease, the use of combined therapy with potassium iodide and bismuth, as advocated long ago by Lesser, may be preferable to treatment with penicillin or arsenicals, since it avoids crises often induced by the latter drugs.

Treatment of Neurosyphilis

Treatment of General Paralytics Followed for More Than Five Years.—A cooperative group[164] evaluated the therapeutic value of penicillin and the possible additive effects of fever therapy in 1,086 paretic patients at eight different hospitals. Of those tested, 629 received penicillin alone; 457 penicillin plus fever therapy. Over 90% were followed for one year or more and 60% for five years or more. Results indicate, in part: Paresis is seen three times as often in men as in women and more than twice as often in whites as in Negroes. Ten to 24 years after infection is the usual incubation period. The trend in treatment is towards penicillin alone, and repository penicillin is as suitable as aqueous penicillin for general paresis. The probable additive effects of fever therapy do not justify its routine use; however, it may be used by the clinician in selected cases. The minimal effective dose of penicillin is not known. Six million units are probably ample. One of three institutionalized paretics may be rehabilitated for work; early diagnosis and treatment produces clinical remission and rehabilitation in over 80% of cases.

Evaluation of the Treatment of Neurosyphilis with Penicillin and Fever Therapy. After reviewing some recently published work on the treatment of neurosyphilis with penicillin, Tempski and his coworkers[165] discuss their own results, obtained at the Dermatological Clinic of the Medical Academy, Lódz, Poland, in 76 cases of neurosyphilis. The patients were followed up for one to four years, with examination of the cerebrospinal fluid (CSF) every 6 to 12 months. Only changes in the CSF were accepted as confirmation of improvement, regardless of changes in the clinical picture. Of the 76 patients, 51 were treated with penicillin only in a dosage of 300,000 units daily to a total of 6, 9, or 12 mega units; all the patients in this group had some organic disorder, such as active tuberculosis or hepatic, renal, or cardiovascular disease, which was regarded as a contraindication to fever therapy. The remaining 25 patients received the combination of fever therapy and penicillin treatment. Of the total of 76, the treatment was unsuccessful in 28 cases (36.8%); 6 patients showed no improvement; 14 very slight improvement; 2 exacerbation and 6 relapsing in respect to CSF changes. The failure rate for the combined treatment was 28%, whereas that for treatment with penicillin alone was 41.2%. The best results were obtained in asymptomatic neurosyphilis, less good results in tabes dorsalis, and the poorest results in cases of cerebrospinal syphilis, and of progressive paresis.

Efficacy of Vitamin B_{12} in the Alleviation of the Lightning Pains of Tabes Dorsalis.—Redmond[166] reports the effect of vitamin B_{12} on lightning pains of tabes dorsalis in six men patients. Each received 1,000μg. daily for 10 days, then twice a week for 10 weeks. After treatment, pain disappeared or became less frequent and less intense; there was a reduction in the amount of analgesic drugs taken to control the pain and increased ability to walk and exercise. In addition, paresthesias disappeared in a number of patients. Redmond concludes that vitamin B_{12} therapy affords the best method of alleviating lightning pains while reducing the use of narcotics to a minimum.

Penicillin Reactions

Many authorities have noted a definite increase in penicillin reactions.[167-169] In fact, the 121 commercially available penicillins appear to be the main producers of trouble in the antibiotic field.[170] Dobson and the group at the Hitchcock Clinic[171] state that almost one-third of all reactions to drugs were instances of penicillin reaction. The six main types of penicillin reactions they observed are: (1) anaphylactic (occurring within an hour after administration); (2) erythema, papulation, and vesiculation of the hands, feet, and groin (occurring 24 to 48 hours after initial injection); (3) urticaria (occurring within five days to several weeks); (4) serum sickness (occurring 5 to 21 days after

injection); (5) contact dermatitis; (6) a miscellaneous group (occurring after incubation period of a week or more), including such conditions as erythema multiforme, erythema nodosum, pityriasis rosea-like id, toxic erythema, and exfoliative dermatitis.

Morton [172] presents a most interesting report on penicillin reactions. He is one of the few workers who has the temerity to give further penicillin after urticarial, serum sickness-like, and even anaphylactic reactions to penicillin. Of 256 patients who received a total of 5,870 injections of procaine penicillin, local urticaria appeared in six, serum sickness-like reactions in six, and anaphylactoid reactions in nine. Six of the nine who had anaphylactoid reactions continued with treatment without further reaction. Skin tests performed in five of these patients with anaphylactoid reactions were negative. Of 147 patients given 3,512 injections of benethamine penicillin, painful induration of the buttocks occurred in 63, localized urticaria in 6, generalized urticaria in 2, and anaphylactoid reaction in 1. It is stated that antihistamine therapy gave adequate control of the reaction and permitted the completion of the daily courses of therapy. Possibly other workers have been too cautious in withholding penicillin from all patients who have had a reaction to this drug.

Sensitivity to Repository Penicillins.—Willcox and Fryers [173] made a detailed retrospective study of the side-effects observed after the administration of 7,300 injections of four repository penicillins: penicillin in oil and beeswax; procaine penicillin in oil with aluminum monostearate; benzathine penicillin, and benethamine penicillin, given to 895 venereal disease clinic patients over an 11-year period. The incidence of "probable" reactions was 2.9% of patients and 0.4% of injections. The incidence of reactions was directly related to the number of injections, the dosage, the duration of treatment, and to previous penicillin treatment. Many more reactions were noted in patients treated for syphilis (multiple injections) than in those treated for gonorrhea (single injection). The incidence of reactions increased with age. The reaction rate in 1956 was not greater than that in 1948 if only the "probable" reactions are considered. Nor was there a significant difference in the incidence of "probable" reactions among the four different penicillin preparations employed. No unequivocal cases of anaphylactoid reaction were observed.

Reactions from Multiple Injections of Benzathine Penicillin G.—The rates and severity of reactions after repeated intramuscular injections of benzathine penicillin G were studied by Sherwood and his associates.[174] Two dosage regimens were used, 600,000 units every four weeks (1,567 men) and 900,000 units every six weeks (1,708 men). No fatal or anaphylactoid reactions were encountered. The cumulative probability of reacting was almost identical, 0.061 (6.1%) in the 600,000 unit group and 0.058 (5.8%) in the 900,000 unit group. When those with reactions were excluded, the probability of reaction decreased markedly in both groups after the first injection and prolonging the interval between injections did not change the reaction rates. It was concluded that the use of repeated intramuscular injections of benzathine penicillin G was a feasible and safe procedure.

The results of a blind study to evaluate local reactions in 320 children (age 3-12 years) 24 hours after injections of one of four preparations at the Pediatric Clinic of Bellevue Hospital Outpatient Department is reported by Krugman and Ebin.[175] All injections were in the buttocks. Results indicated that local tolerance to benzathine penicillin G (9,600,000 units) was considerably increased when combined with 5 mg. of prednisolone, or an equal dose and volume of aqueous procaine penicillin. Penicillin preparations used and per cent of severe local reactions to each were: (1) benzathine penicillin G, 600,000 units in 1 ml. (54% reactions); (2) benzathine penicillin G, 600,000 units with 5.0 mg. prednisolone added in 1 ml. (9% reactions);

(3) benzathine penicillin G, 600,000 units plus aqueous procaine penicillin 600,000 units in 2 ml. (11.5% reactions); (4) aqueous procaine penicillin, 1,200,000 units in 2 ml. (4% reactions). The percentage of mild local reactions was the same for all preparations (11 to 12% reactions).

Björnberg and Selstam[176] report nine cases (six women, three men) of acute transient psychotic reaction which occurred during or immediately after intramuscular injection of procaine penicillin in aqueous suspension at the Skin Clinic, Holtermanska, Sjukhuset, Gothenburg, Sweden, during 1953-1956. Seven of the nine cases were syphilitic. Manifestations included primarily conviction of imminent death, and visual and auditory hallucinations; other disturbances were a sense of oppression, disorientation, material agitation, transitory blindness, and high facial color. No signs of peripheral circulatory insufficiency were noted. Mental symptoms were observed in three patients for a few months after the reaction. All reactions occurred during a long series of daily injections, the earliest being on the 9th day and the latest on the 56th day after starting the course, and the same preparation was given subsequently with no side-effects. It is concluded that the reaction was of a toxic nature on the central nervous system, caused by intravascular penetration of the injected procaine penicillin G.

Anaphylactic Reactions.—Anaphylactic (shock) reactions to penicillin are increasing.[177-181] Both local and oral administration of penicillin have been followed by this serious reaction.[182-184] It has also occurred in a patient receiving steroid therapy.[185] Prophylaxis of this reaction is possible by the application of drops full strength (300,000 units per cc.) of procaine penicillin G to a scratch in the skin or into a conjunctival sac. Smith[186] and Cazort and Johnston[187] use 200,000 units of soluble penicillin in 1 cc. of 50% each of glycerol and saline.

Teigland,[188] in an effort to prevent these serious reactions, suggests that a careful history of all allergies and any previous reactions is helpful. Penicillin should be avoided when it is of no special value. He believes that negative skin tests are no assurance. Penicillin should be given only when epinephrine is immediately available. His suggestions for treatment are: (1) application of tourniquet above the injection; (2) epinephrine (1:1,000 aqueous solution) given subcutaneously in doses of 0.5 to 1.0 cc. Repeat within a few minutes; in emergency give intravenously; (3) antihistamines (25 to 50 mg. of Benadryl or Pyribenzamine, or 10 to 20 mg. of Chlor-Trimeton Maleate) given intravenously, using only material labeled for intravenous use; (4) in cases of marked wheezing and dyspnea, the use of aminophylline (0.25 to 0.5 gm. in 10 cc. intravenously); (5) hydrocortisone in 100 mg. doses given as soon as possible; (6) if cyanosis is present, use of oxygen; (7) if shock is prolonged, use of plasma or blood. Norepinephrine can also be used to maintain blood pressure.

Penicillinase in the Treatment of Penicillin Reactions.—Minno and Davis[189] found that penicillinase could effect relief dramatically within a few hours in several cases, but it is not a panacea for all penicillin reactions. The use of penicillinase in the treatment of hypersensitivity reactions to penicillin is based on the logical knowledge that circulating penicillinase reduces all demonstrable penicillin blood levels to zero for prolonged periods of time, thus rendering the penicillin nonallergenic. The reactions to benzathine penicillin G responded on the average as quickly as those to procaine penicillin G. The usual dose administered was one million units of penicillinase in 2 cc. of sterile distilled water, intramuscularly. In those instances of severe reactions wherein response was not definitely beneficial within 48 hours, injections were repeated in 48 hours. Becker[190] also treated 46 patients with penicillin reactions with penicillinase. Twenty-four were treated with intramuscular penicillinase alone with uniformly good results. The other 22 patients had previ-

ously received or were given concomitant therapy with various antihistamines and/or corticotropin and steroids. In 20 of these the favorable clinical response seemed to be directly due to the penicillinase. The two failures were given the penicillinase weeks to months after the reaction started. In one of the good responses (actually fair) the penicillinase was given two weeks after the onset of the reaction. No significant ill effects due to penicillin were noted.

Pabalate in the Treatment of Penicillin Reactions.—Warren [191] used Pabalate (a composition of 300 mg. each of sodium salicylate and sodium *p*-aminobenzoate with 50 mg. of ascorbic acid) in the treatment of penicillin-sensitivity reactions. He could not state whether one or the synergestic action of the two components of the preparation produced the good results.

Syphiloid Diseases

Many new reports dealing with the syphilis-like (nonvenereal syphilis) diseases continue to appear. The World Health Organization is still responsible for the bulk of the studies. The major lines of interest are epidemiological and eradicative procedures and results. New re-evaluation of well known clinical manifestations occupy the attention of some of the students of this aspect of medicine.

Epidemiology of Endemic Syphilis.—Guthe and Luger [192] review the present knowledge of nonvenereal syphilis on the basis of recent experiences in underdeveloped communities of Bechuanaland, Bosnia, Iraq, Syria, and other areas where "endemic" syphilis has been a health problem. Some 25% to 65% of the people in these areas have been found reactive to serologic tests for treponematosis using cardiolipin-lecithin antigens. Over the centuries, transmission has been facilitated, a characteristic age pattern of onset has resulted, T. pallidum has adapted itself to the immunological and other conditions of the host, and differences in the frequency of disease manifestations as compared to venereal syphilis have resulted. Particular reference is made to the absence or rarity of congenital and neurovisceral manifestations in endemic-syphilis areas. Guthe and Luger believe that the common basic "vector" of endemic syphilis is the hands of children, which, by reflex action, are put to the mouth, thus systematically favoring the transfer of T. pallidum from early infectious lesions to the hands and faces of other susceptible children. Transfer may also take place through contaminated drinking flasks, cups, and other communal utensils. The frequency with which this may happen varies with local conditions, habits, and customs.

The Transmission of Yaws in Nature.—Hackett,[193] considering the factors which may play a part in the transmission of yaws in nature, suggests that some form of contact must be the essential factor, aided by preparation of the skin by minor injury. It is suggested that treponemes are dispersed on the skin of the infectious patient, at least around the papillomata. The itching of the papillomata causes the patient to rub the surrounding skin with the finger tips, which thus become contaminated with treponemes. In children, among whom yaws is most frequently transmitted, the closest contact is by hand to hand. When a person receives a minor injury to any part of the body, the almost automatic response is to rub the area involved, and the area below the knee is most exposed to minor traumata in partly-clothed rural populations. The rubbing of minor injuries with the finger tips contaminated with treponemes implants the treponemes on abraded skin through which entry to the body is effected. This way of transmission would explain the high prevalence of initial lesions on the lower limbs. Warm, humid conditions and poor hygiene would favor this means of transmission. Some studies are necessary and are suggested to investigate the soundness of this postulation.

Campaigns [194-196] against endemic syphilis have been reported on from Serbia,[197] Nigeria,[198] Liberia,[199] Western Samoa,[200] Brazil,[201] and the other Americas (Mexico,

Caribbean, and South America),[202-204] and Haiti.[204-206]

Late Manifestations of Yaws.—From an extensive study of 121 patients affected with late yaws from the northeastern region of the state of Minas Gerias (Brazil), Furtado[207] abstracts his conclusions. Of particular interest is the section devoted to the differential diagnosis of yaws and syphilis. Furtado thinks the following points may be very valuable: (1) patient's residence in an endemic zone; (2) unquestionable history of yaws infection in the past; (3) coexistence with certain cutaneous lesions, since keratodermia palmaris et plantaris is common in yaws and rare in syphilis, and gangosa and juxta-articular nodules are commoner in yaws; (4) coexistence of the late cutaneous manifestations with bone and joint lesions which are more extensive and more frequent in yaws (10%-15%) than in syphilis (5%-10%); (5) reactivity of serologic tests for syphilis is practically 100% in yaws as compared with a lower percentage in syphilis (50%-80%); (6) the absence of involvement of the internal organs in yaws in contrast with the incidence of neurological (3%-10%) and cardiovascular (5%-10%) manifestations among syphilitic patients.

Leprosy and Yaws.—Although the causative agents of yaws and leprosy are entirely distinct, Davey[208] points out that the two diseases have a number of points of contact as regards clinical appearance, epidemiology, and control. Usually the differential diagnosis of yaws and leprosy presents little difficulty. The typical case of either disease is not likely to be confused with that of the other, and even with only simple laboratory facilities, mistakes should not be made. The two diseases may, however, be present in the same patient. The most difficult and fascinating problems in distinguishing leprosy from yaws arise in the important group of indeterminate lesions which link one main form to the other, rather than in relation to typical lepromatous or tuberculoid leprosy. Nerve involvement is variable but never marked in the lesions. Every gradation of change may be encountered from atypical tuberculoid on the one hand to early leproma on the other. With such a variety of appearances it is not surprising that the macules of yaws should sometimes be simulated.

The Etiology of Dupuytren's Contracture in Eastern Nigeria.—According to Walters and Zahra[209] contracture of the fingers into a flexed position, but with the terminal interphalangeal joints extended, is a clinical problem encountered in yaws endemic communities. This study by Walters and Zahra was made during the course of the (WHO/UNICEF joint assisted) mass treatment campaign in Nsukka. The prevalence of the contracture, which they call Dupuytren's contracture, became greater with increasing age. In one area, in children under 10 years of age it was less than 1%, and above that age it increased from over 5% in the 11-18 age group and to 9% in those over 18 years old. In another group of villages, no cases were seen in persons under 16, and in adults only 0.5% was found. The possible cause of these contractures is discussed and the development of the bilateral deformity "quite early in childhood would appear to exclude trauma." The workers found that where yaws prevalence is high the contracture is frequent. "It is claimed that the results of the serological survey confirm the epidemiological evidence that yaws plays the leading etiological role in the development of Dupuytren's contracture among the people" of the villages studied. It is not stated to which stage of yaws, that is, early or late, these contractures belong, or what the pathological changes are that lead to them. There is no doubt that these contractures occur in yaws-endemic communities but not necessarily with equal frequency in populations with similar prevalence of clinically active yaws. Insufficient data on the patients in the serological studies are given to allow an adequate re-study to be made, but it is doubtful if it is wise to use the data in the way that these investigators have done. They have shown that in populations with

little yaws there are few finger contractures, and vice versa, but correlation does not necessarily imply causation, and in the former populations there are other variants than the prevalence of yaws, such as social advancement. It is hoped that this report will stimulate others to make further studies on the etiology of the finger contractures that occur in people among whom yaws is endemic.

Yaws-like Disease.—Prabhakar [210] of India states that he commonly saw patients with granulomatous lesions resembling those of yaws and having a positive Wassermann reaction in the venereal disease clinic. Seventy villages with a population of 25,361 were surveyed, and about 5% of the population were found to be affected by this condition. The incidence, however, varied from village to village. The patients were divided into three groups according to the type of lesions present. In the first group, early lesions consisting of granulomatous nodules on different parts of the body, pain, and tenderness in the bones and joints due to periostitis and arthritis, pyrexia, and swelling of regional lymph nodes were seen. The second group had active lesions with gummatous swelling and ulcerative and desquamatory lesions, particularly plantar keratodermias. Bony deformities were present, due to various degrees of thickening of the long bone. The third group showed healed lesions with typical pigmentation, shining scars on the skin, and stationary bony deformities. On the whole, granulomatous lesions were the most important lesions and were seen in 71.5% of the persons affected. They appeared on many parts of the body but rarely on the feet and the scalp. The ulcerative skin lesions were mostly seen as keratodermias of the sole. Bony deformities were common in the extremities—more in the legs than in the arms. Boys were more frequently attacked than girls, and the lesions remained generally benign. Relapses, however, were frequent in children. Active lesions were noticed in 5.3% of the boys up to 10 years of age. In the age group 11 to 20, the number of patients with active lesions increased to 21%. In the next decade, active lesions were more frequent (40.3%), and women were more commonly affected than men. In the next two decades men were more frequently attacked by the disease than women.

Control of Syphilis

Earlier in this review a certain amount of evidence was cited to indicate that syphilis continues to be a disease problem of some importance. It is noteworthy that in certain quarters educational efforts, serologic surveys, and other activities dealing with case finding and case holding are still going on. Sometimes help in the program may come from unexpected sources, as was the case reported in *Time* [211] in which in Los Angeles a telephone gag to "Please call Mr. Smith at Mutual 6256" resulted in 70 V. D. victims daily calling for help—a result which the expenditure of thousands of dollars in regular propaganda could not have accomplished.

Laurie [212] reports on a pilot program for control of the venereal diseases in East Africa. The Bahaya tribe in the Bukoba District of Tanganyika was selected because it was felt that the marked decrease in the population of this tribe might be ascribed in part to the venereal diseases. In a selected group of over a thousand men and over five hundred women, gonorrhea was present in 46% of the men and 19% of the women. Primary or secondary syphilis was present in 19% of the men and in a smaller percentage of the women. In addition, there were many seroreactors with no clinical evidence of disease. Laurie points out that in this group yaws, malaria, and leprosy may have caused confusion. From the experience gained in this pilot study, he feels that large scale control measures are likely to be successful in East Africa. Hecht [213] complains that the present teaching of venereal diseases (syphilis) in American medical schools is not sufficient. He feels that courses on venereal diseases should be compulsory for practi-

tioners. He also makes practical suggestions for the education of lay persons on these diseases. According to a survey conducted by Dr. Samuel D. Allison,[214] acting chief, Bureau of Venereal Disease Control, Honolulu, Hawaii, there is "some degree of teaching" about VD in all of the forty-eight states. However, in eleven states there is "only incidental teaching." Most public health and school administrators contacted in the survey recognized education as a "vital component" of any VD control program. Twenty states indicated that VD teaching is included in health courses; 14 states integrate VD into their physical education classes; 13 in their biological courses; 9 in home and family living; 8 in home economics; and 8 in social studies. Main obstacles to school instruction programs in the VD area were cited as public opposition, lack of adequately-trained personnel, and lack of funds. A number of laboratory courses were offered during 1957-1958 at the Venereal Disease Research Laboratory. This Laboratory has also afforded a variety of field consultation services to the States.[215] It also evolved a serology-control program to assist state laboratories in attaining and maintaining a high level of efficiency in serologic testing.[216] New Mexico[217] found the film, "The Invader," to be an integral part of any venereal disease educational program. The role of the serologic laboratory in the diagnosis of syphilis has been emphasized by several authorities.[218-226]

The problem of syphilis in teen-agers has received attention. St. Louis'[227] second Venereal Disease Study was conducted with the objective to "gain more knowledge of the social, cultural, and personality factors that lead teen-agers to such sexual behavior which may increase the possibility of venereal disease."

Venereal Disease in Women Prisoners.—As founder of the venereal disease clinic in a large British prison for women, Keighley[228] presents the results of her studies in women prisoners. The prevalence of syphilis has declined from about 9% of the prisoners in 1951 to a little over 5% in 1956. In prostitutes syphilis prevalence ranged from 13½% to 16%. Over one-half of the prostitutes examined gave a history of previous treatment for venereal disease. Most of the prostitutes were under 25 years of age. Keighley discusses the difficulty of rehabilitation of prostitutes, except for those who are apprehended within the first few weeks or months of beginning their trade.

The legal aspects of syphilis control have been studied far and widely. Tottie[229] points out that when the Swedish law against propagation of venereal diseases came into force on Jan. 1, 1919, there was a greater number of cases of syphilis, ulcus molle, and gonorrhea. Therapy at that time was of limited value. Since then the advances in venereology have been great, but in spite of all this there are still many cases of venereal disease. He believes the Swedish Lex Veneris will still be necessary, and, if applied in the right way, it will serve its purpose in the fight against venereal diseases. In Italy[230] Law No. 837 of July 25, 1956, as reported in International Digest of Health Legislation, provides among other items for: compulsory treatment, free examination and treatment, compulsory reporting by physicians, and hospitalization of the patient, if necessary to prevent spread of the disease; serologic examination for syphilis in all cases where certification of physical fitness is obligatory, when requested by any person intending to marry, by members of the armed forces upon commencement, upon discharge from military service, and for prisoners or minors during their period of detention; and the establishment of appropriate outpatient clinics and of Government clinics serving port workers and mercantile marine personnel. The publication of advertisements of remedies or method of treatment of venereal diseases and sexual disorders is prohibited; and the responsibility for control, promotion, and coordination of publicity on the danger of venereal disease is vested in the Office of

the High Commissioner for Hygiene and Public Health.

The premarital and prenatal laws are being widely applied and with general approval, suggestions for improvement,[231-234] or some opposition.[235]

An outstanding contribution during this review period is the influence of changes in sexual behavior on venereal disease control. This is especially indicated by the papers on homosexuality. Because of the importance of this development, considerable space is given to it here. Gryson[236] analyzes the various aspects of sexual behavior as it has evolved in modern society and related to the fight against venereal diseases (particularly syphilis). Venereal disease control encompasses a judicial, a medical, and a moral aspect. While prostitution has been legislatively abolished in almost all civilized nations, it still exists in a variety of forms, discussed by Gryson. Belgium still contains 50,000 prostitutes among 9,000,000 inhabitants; Kinsey reports about 69% of white men had relations with prostitutes. More is required than judiciary processes. Many aspects of the Belgium law are discussed, as are problems in connection with the control of VD from the medical aspect. The need for sex education has been admitted among nations, but all debate the methods of application. The need among adults is recognized and particular emphasis is suggested concerning sex education among the youth, beginning with the child before puberty. This should be done gradually and individually. This education should not be limited to the physiological aspect but should embrace sentimental, social, and religious concepts to prepare the person for the psychologic aspects of marriage and family life.

Homosexuality: An Analysis of 100 Male Cases Seen in Private Practice.—Of 5,000 psychiatric patients seen in private practice by Curran and Parr,[237] 100 men (5%) between the ages of 16 and 69 years, and 7 women (0.3%) were homosexuals. The 100 men were studied retrospectively and so far as possible by follow-up. All but 11 of the 100 patients admitted to one or more homosexual acts with others since adolescence. Many were highly promiscuous, and most of them were quite active, the practicing group committing at a conservative estimate an average of at least 10 homosexual acts each annually. There was no evidence that those who admitted to sodomy differed from other practicing homosexuals in social or economic success, stability or social worth, or that the continent group differed from practicing homosexuals in these respects. Of the 100 patients, 43 had an associated psychiatric syndrome (often minimal), a neurotic, inadequate or "sociopathic" personality, or a combination of both. Six additional patients gave a history of psychiatric trouble in the past. Thus, despite the probability that any group of homosexuals referred to a psychiatrist might be expected to be heavily weighted in the direction of psychiatric abnormality, 51 were considered to be free from gross personality disorder, neurosis, or psychosis during their adult lives. Of the 100 men, 17 were pedophiliacs, i. e., they were sexually attracted to prepubertal boys. They constituted a distinct group and only 2 committed homosexual acts with both adult men and prepubertal boys. There was no evidence of those preferring adults subsequently seeking boys—the "rake's progress." Of 59 patients from whom relevant information was obtained in the follow-up, a change toward heterosexual preference was noted in 9, while 3 became more homosexual, and 47 were unchanged. Only 1 of 24 patients originally regarded as "100% homosexual" reported a change in the direction of heterosexuality. Twenty-five patients treated psychotherapeutically derived no apparent benefit in terms of changed sexual preference or behavior as compared with 25 matched patients not so treated. No difference between the two groups could be discerned as regards change in sexual orientation, discretion, or control. Twelve of the treated patients, as compared to 8 of the untreated patients, appeared to come to better terms with their problems at a

subjective level, but increased overt activity was sometimes noted after treatment. None of these differences were statistically significant.

Homosexuality and Prostitution.—In April, 1954, the Home Secretary (England)[238] appointed a committee to consider the law and practice relating to homosexual offenses, the treatment of persons convicted of such offenses by the courts, and the law and practice relating to prostitution and solicitation for immoral purposes. In its report the committee (with one dissentient) recommends that homosexual behavior between consenting adults in private should no longer be a criminal offense, that questions relating to consent and in private be decided by the same criteria as apply in the case of heterosexual acts between adults, and that the age of adulthood for the purposes of the proposed change in the law be fixed at 21. In coming to these conclusions the committee states that it has considered the degree to which the criminal law should concern itself with sexual behavior and believes that it is not the function of the law to intervene in the private lives of citizens or to seek to enforce any particular pattern of behavior concept except insofar as this may be necessary to preserve public order and decency, to protect the citizen from what is offensive or injurious, and to provide sufficient safeguards against the exploitation of others, particularly those who are specially vulnerable. The committee recommends that the law relating to living on immoral earnings be applied to the earnings of men as well as women prostitutes and that the law relating to brothels should apply to premises used for homosexual practices. So far as treatment is concerned, the committee is not in favor of castration but recommends that the present ban on the use of estrogens in prisons be removed in those cases in which the prisoner desires it, and the medical officer considers that it would be beneficial. The committee recommends research into the cause of homosexuality and the effects of various forms of treatment. It also recommends educative measures for medical students, clergy, and probation officers; restricted press reporting; and more care in the selection of teachers, youth leaders, and others in similar positions of trust. In the case of prostitution, the committee recommends that the maximum penalties for street offenses be increased and that a system of progressively higher penalties for repeated offenses be introduced. The present maximum is $5.60 for the first or any subsequent offense. The committee recommends that the maximum penalty for a first offense should be a fine of $28; for the second offense, a fine of $70; and for a third or subsequent offense, three months' imprisonment. A further recommendation is that the law relating to street offenses be reformulated so as to eliminate the requirement to establish annoyance, as is the case at present. The committee rejects licensed brothels as an alternative to the present state of affairs.

The Esoteric Male as a Focus for Spread of Venereal Disease.—Goodman[239] brings to the medical literature the subject of the role of the homosexual man in the spread of venereal diseases. The emphasis on the woman as a source of venereal disease among men reduces the important place the esoteric (homosexual) man has in dissemination of newly-acquired syphilis. Goodman feels that the male prostitute should be given equal status with the female prostitute. Likewise, he suggests the routine prophylactic administration of penicillin for men brought to official attention by arrest for sex perversion.

Venereal Diseases in Homosexuals.—Hecht[240] reports on six patients with venereal diseases or with fear of having contracted some by homosexual contact. He calls attention to the fact that homosexual practices are not as rare as our moral standard would claim. Procedures other than the "normal" ones practiced often even in heterosexual relations can be followed by extragenital infection with venereal diseases. Syphilis is still one of the most frequent diseases in general practice and

should be suspected and recognized without laboratory tests. The latter should be used to confirm the clinical diagnosis. Hecht believes that normal and pathological sexual life should be taught in all medical schools.

The Management of Venereal Diseases in Ports: An International Survey.—Throughout history, venereal diseases have been associated with maritime activity, and the role of the sailor as a frequent carrier of these "water-borne" infections is still significant. In venereal disease-control both seafarers and venereal foci in ports should receive special attention. The study by Willcox and Guthe [241] is based on questionnaires which were answered concerning treatment centers in 171 ports or large cities in 25 maritime countries. It was found that there is an ever-increasing use of penicillin alone in port clinics for the treatment of early syphilis. Of 167 schedules reported, penicillin alone was used in 83.2% and penicillin plus metal in 16.8%. Penicillin therapy alone was employed for late syphilis in 73.1% of the total schedules report. With the introduction of longer-acting penicillin preparations, the duration of penicillin treatment for all types of syphilis showed a tendency to rise. The highest figures came from Europe. For example, penicillin treatment of secondary syphilis lasted for more than three weeks in 28.6% of European clinics and for more than four weeks in 19.0%, compared with 5.0% and 1.7% respectively in clinics in the United States of America. Of little concern to the individual sailor with syphilis, but very important from a public health viewpoint, is the treatment of contacts. The treatment of some contacts has been widely accepted in Southeast Asian, and Central and South American regions, but in only a few of the clinics of the Mediterranean and European areas.

Supervision of Field Personnel.—Ways and means of supervising the personnel of field teams in health surveys are described and discussed by Fausto,[242] including the relation of the supervisor both to the administrative personnel and to those under him. Field personnel should never be aware of any dissension between the supervisor and the administrators. Rapid transport for supervisors of field personnel is one of the essentials if the element of "surprise" is to be preserved. The training of the supervisor and his capacity for work and action should be superior to that of those being supervised. Remuneration must be sufficient to compensate for additional responsibilities and give incentive to perform well. The ability to get along with those under their supervision, fellow supervisors, and administrators is prerequisite to promotion.

The Role of the Private Physician in Venereal Disease Epidemiology.—Nelson[243] summarizes preventive measures available and their application in the control of infectious syphilis and gonorrhea as to the agent, the host, and the environment with particular reference to the need for the private physician's cooperation. Mechanisms of case finding are divided into four main groups: (1) a high index of suspicion; (2) screen examinations; (3) education; (4) contact investigation. The first three pertain to mass aspects and the role of the private physician is self-evident; in the fourth (individual case finding) the potential contribution of the private physician has not been realized. The time required for the doctor to develop an understanding and cooperative patient will pay big dividends in establishing names and locations of contacts. An epidemiological investigation made in New York State and in British Columbia are discussed, together with the responsibilities of the private physician in contact investigation. It is concluded that private physicians must be made aware of their potential contribution to contact investigation, and the magnitude of the undiagnosed reservoir of infectious cases (especially gonorrhea in women) and must acquire new skills in interviewing, particularly male gonorrhea patients for female contacts.

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Contributions of Basic Science to Modern Medicine

Mechanisms of Urinary Concentration and Dilution

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Introduction

The happy facility which enables the organism to vary, over rather wide ranges, the relative proportions of urinary water and solute is a phenomenon of manifest teleologic advantage and constitutes perhaps the major line of defense with regard to homeostasis of volume and tonicity of the body fluids. The osmotic pressure of the extracellular fluids, and presumably of the cells they bathe, is punctiliously guarded at values of approximately 280 to 300 mOsm. per liter.* The cellular milieu of the human kidney, however, must somehow cope with the fluid contents within its tubules, which between the extremes of maximum diuresis and antidiuresis ranges from under 50 to more than 1,300 mOsm. per liter, that is, roughly one-sixth to over four times the osmotic pressure of the plasma. The kidney of other mammals may perform even more spectacularly: the urine within the collecting tubules of certain desert rodents that subsist largely upon dry diets may attain concentrations 17 times that of the plasma.[1] The flexibility of the urinary function of the kidney, and the mechanisms underlying it, have understandably been subjected to considerable experimental scrutiny. The results of these experiments and the more significant and provocative conclusions deduced therefrom constitute the subject matter of this review.

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* The more accurate designation of osmotic activity is milliosmols per kilogram of H_2O, since cryoscopic techniques determine osmolality (osmols per kilogram of pure solvent) rather than osmolarity (osmols per liter of solution). Popular usage has established milliosmols per liter, which, although technically incorrect, has been retained herein to indicate osmolality. Relative dilution of biological fluids in general minimizes the discrepancy between these two indices.

The Classic Concept

The most popular and, until very recently, the most plausible theory of the mechanisms of urinary concentration and dilution, was that of Homer Smith and his co-workers, Wesson and Anslow.[2-5] Because it is so firmly established, and because it offers a most logical and useful frame of reference in which to orient quantitative thinking about renal processes, this hypothesis and the more pertinent experimental observations from which it derives will be reviewed in some detail before considering the more recent and divergent concepts.

Functional Geography of the Nephron.—Proximal Tubule: The composition of the urine finally reaching the bladder depends upon the specifically renal operations of filtration at the glomerulus and reabsorption from and secretion into the tubules of water and solutes. The structural variations along the course of the individual nephron are such as to imply specific functional properties for each discrete segment. Current concepts of the functional geography of the nephron may be considered to originate largely from the work of Richards and

Walker and their colleagues.[6] Utilizing micropuncture and microanalytic techniques, these authors established that the fluid in Bowman's capsule of the amphibian kidney was essentially free of protein and that its composition was characteristic of an ultrafiltrate of plasma with respect to osmotic pressure, electrical conductivity, pH, glucose, creatinine, inulin, and electrolytes.[7-13] Extending these techniques from the amphibian to the mammalian kidney, Walker et al.[14] were able to puncture and analyze the fluid from various portions of the proximal tubule of the rat, guinea pig, and opossum. They determined that by the end of the proximal tubule (*a*) virtually all of the glucose and phosphate of the glomerular filtrate had been reabsorbed; (*b*) the volume of the glomerular filtrate had been reduced by approximately 80%; (*c*) the creatinine concentration had increased almost fivefold, but (*d*) the *total* osmotic activity remained equal to that of plasma. Since creatinine is apparently neither secreted into nor reabsorbed from the tubule to any significant extent, intraluminal concentration of this substance can be achieved only by the removal of water. Net osmotic activity, however, did not change; reabsorption of water, therefore, must have been accompanied by an amount of solute in such proportion as to maintain isotonicity between the reabsorbate, the fluid residual in the tubule, and the plasma. Since the activity of sodium and its associated anions contributes the bulk of osmotic pressure of plasma and hence of the glomerular filtrate, it follows that proximal reabsorption of water proceeds together with sodium salts in roughly their concentration in the extracellular fluids.

Further information about the nature of these proximal processes was contributed by Wesson, Anslow, and Smith.[15,16] These workers induced osmotic diuresis in dogs by administering hypertonic solutions of mannitol, a nonreabsorbable solute, intravenously. The resultant diuresis approximated, per minute, two-thirds of the glomerular filtration rate (GFR); in man, this would correspond to a urine flow of almost 80 ml. per minute. Such a rapid flow seemed to preclude any marked modification by more distal structures, so that the final bladder urine was assumed to represent the composition of the fluid at the end of the proximal segment or thin limb.[2] During this rather energetic performance, the osmotic pressure of the urine was almost equal to that of the plasma. The major share of the osmotic pressure of this virtually isosmotic urine was contributed by mannitol, hence the concentration of sodium was considerably below its concentration in plasma, the difference reaching 60 mEq. per liter in some experiments. The excreted urine contained up to 65% of the filtered water but no more than 27% of the filtered sodium. The fact that proportionately much less sodium than water reached the bladder implies that proximal reabsorption of this ion is independent of the reabsorption of water, while the lowered urinary concentration indicates that sodium reabsorption proceeds against a concentration gradient and is most likely an active process.

Based largely on the foregoing, the concept of Smith and of Wesson and Anslow concerning events in the proximal segment is (1) a primary active removal of sodium followed by (2) an obligatory passive diffusion of water along the osmotic gradient resulting from the active movement of solute, so that the osmotic urine-to-plasma ratio (U/P)† remains close to unity. Thus, the net accomplishment of operations within the proximal tubule is to return to the circulation the bulk of the filtered water and solutes which metabolic necessity dictates should not be eliminated. This process, aptly referred to by Robinson[17] as "routine conservation," reduces the volume

† The U/P ratio expresses the relationship between the concentration of a substance in the urine and its concentration in plasma, affording an index of the extent to which a substance is diluted (U/P<1) or concentrated (U/P>1). An osmotic U/P of 1, of course, indicates isotonicity of urine and extracellular fluid.

of the glomerular filtrate by about 80%-85%.

Loop of Henle: The specific functions of the loop of Henle have long eluded unequivocal definition. A thin limb appears in birds and mammals, the only vertebrates capable of elaborating urine hypertonic to plasma, and there appears to be a positive correlation between the length of the loop with ability in a given species to elaborate concentrated urine.[18-20] Indeed, in 1933, Burgess, Harvey, and Marshall[21] proposed that the action of the neurohypophysial hormones in promoting reabsorption of water was exerted upon the thin limb and regarded this segment as the site of urinary concentration. This view was discarded, largely because of the argument that the epithelium of the loop is too thin to perform significant osmotic work,[22] although it has long been recognized that the very thin epithelium of frog skin and fish gills may perform rather remarkable amounts of work against osmotic gradients.‡ Recently, however, there has been a resurgence of interest in the loop of Henle, and newer work indicates that it most likely does play a critical role in the formation of hypertonic urine; this will be discussed more fully in a later section of this review. According to the theory presently under consideration, the thin limb serves as an area of osmotic equilibration: the active process in the proximal tubule, primary movement of sodium, might slightly outstrip the passive reabsorption of water, rendering the fluid hypotonic; the thin limb, composed of epithelium permeable to water, would allow diffusion of water so that isotonicity could be reestablished.

Distal Tubule: The processes of glomerular filtration, proximal reabsorption and equilibration in the loop of Henle, resulting, presumably invariably, in an isosmotic fluid, would seem to be fixed and, in an osmotic sense, unselective. To the distal tubule and collecting duct, then, in this scheme, are detailed the discriminatory mechanisms which determine the ultimate concentration or dilution of the urine. In man, the urine flow may range from less than 0.5 ml. per minute under conditions of dehydration to over 20 ml. per minute during maximal water diuresis. This latter figure represents in normal man about one-sixth to one-eighth of the glomerular filtration rate, a value not exceeded even in severe diabetes insipidus,[24-26] and affords clinical confirmation of the calculation by Walker et al.[14] that about 85% of the glomerular filtrate is reabsorbed before it enters the distal system. Reduction of urine flow to minimal rates implies potential reabsorption within the distal system of about 19 ml. per minute, an operation Smith calls "facultative reabsorption," mediated largely under the influence of antidiuretic hormone (ADH) of the posterior pituitary gland, and implying, contrary to the "obligatory reabsorption" in the proximal system, that the movements of solute and water are not always isosmotic.

The isotonic fluid in the distal system can be rendered hypotonic by one of two conceivable mechanisms: One is the addition of water without solute to the tubular fluid, and the other is the removal of solute without water from the tubular fluid. Despite the arguments of Brodsky and his colleagues in favor of tubular secretion of water,[27,28] there is no conclusive evidence that such does occur, and several reasons have been presented[4] for regarding this as an unnecessary and at present untestable hypothesis. That the urine, during water diuresis in circumstances where retention of sodium is maximally stimulated, may be virtually sodium-free argues strongly for

‡ The finding by Walker et al.,[14] in three punctures of the distal tubule of concentrating rat kidneys, that the fluid therein may be somewhat hypotonic to plasma, indicating that the filtrate which has already traversed the loop of Henle is not concentrated, has been occasionally brought forth as further supporting argument against the idea that concentration of the urine occurs within the loop. Because of the small number of observations, the authors were quite cautious in their interpretation, and these findings have been largely ignored. The validity of the results has recently been confirmed by Wirz,[29] and their implications will be discussed later.

a distal process for the removal of osmotically active solute and implies an active transport of such solute against even greater chemical and osmotic gradients than obtain during proximal reabsorption. The epithelium of the distal tubule, in the absence of any activity of ADH, i. e., in sustained water diuresis or in diabetes insipidus, is virtually waterproof,§ and so water is restrained from following in the wake of the actively transported sodium. For the first time, then, water is retained in the tubular lumen without being completely obligated by an equivalent amount of osmotically active solute. This is not to imply that there is no osmotic activity in the tubule. Urea and other organic metabolic end-products are reabsorbed only to a small and variable extent as the glomerular filtrate traverses the nephron; these waste products must be excreted. Since even large undissociated molecules exert some osmotic activity, one can conceive of a dilute urine as composed of two moieties: a small volume of isosmotic fluid, containing the solutes that were not reabsorbed, plus a much larger amount of osmotically unobligated water, so-called "free-water," resulting from the abstraction of sodium and attendant anions. It is this "free-water," that is, water from which a considerable amount of solute has been removed, that renders the glomerular filtrate hypotonic to the plasma and accounts for the dilution of the urine.

In order to afford a more quantitative basis for the exploration of the renal events concerned with concentration and dilution of the urine, Smith, and Wesson and Anslow[4,5] divide the urinary water into several fractions as shown in the following formulas:

$$C_{osm}=\frac{U_{osm}}{P_{osm}}\cdot V \quad (1)$$

$$C_{H_2O}=V-C_{osm} \quad (2)$$

$$T^c_{H_2O}=C_{osm}-V \quad (3)$$

V represents urine flow in milliliters per minute, and U_{osm} and P_{osm} represent the osmolal concentrations of urine and plasma, respectively, as determined cryoscopically, generally by means of freezing-point depression. The first fraction is the *osmolal clearance*, C_{osm}, determined, in accordance with the general clearance method, as shown in Formula 1. This represents the volume of urinary water required to contain the urinary solutes in a concentration isotonic with the concomitant plasma, so that U/P=1. The second fraction is the net excess or deficit of water in the urine over and above the osmolal clearance. This is referred to as the *free-water clearance*, calculated as shown in Formula 2, which will be positive under conditions of water diuresis in the absence of ADH and negative in antidiuresis under the influence of ADH. Rather than speak constanty of a negative free-water clearance, the deficit of water resulting during the excretion of hypertonic urine is referred to as $T^c_{H_2O}$, derived as shown in Formula 3. It is obvious that $V=C_{osm}+C_{H_2O}$ when the urine is dilute, and $V=C_{osm}-T^c_{H_2O}$ when the urine is hypertonic.

It should be emphasized that these divisions are purely mathematical and are not meant to imply that the urine is in fact discretely fractionated in the functional operations of the nephron. This division is of help, however, in attempting to assess the actions of the tubules. Thus, for a given amount of solute in the urine, by means of these calculations one can extrapolate to determine the amount of water required for the isosmotic excretion of this solute. Any difference between this derived value and the actual volume of urine excreted affords some quantitative idea of what might have happened to an isosmotic filtrate presented to the distal system.

In summary, the process of urinary dilution may be visualized as follows: The glomerular filtrate, considerably reduced in bulk following the operations in the proximal system, but still isosmotic, is presented to a site in the distal tubule which is virtually impermeable to water. Sodium salts are actively removed at this locus, leaving osmotically free water in the lumen, which renders the filtrate hypotonic to the plasma and results in a dilute urine. Implicit in

§ Orloff and Walser[3] have indicated that even in the absence of ADH it is doubtful that the tubular membrane completely restricts the movement of water. The transport of solute, however, so far outstrips that of water that, in explaining the process of urinary dilution, it is not unreasonable for the present to regard the tubule as virtually water-impermeable.

this postulate is the dependence of urinary dilution upon the delivery to the diluting site of sodium and its salts: If none were delivered, none could be reabsorbed, and no free water would be left behind to effect dilution of the urine. This may in part account for the difficulty in gross water diuresis experienced by patients whose body stores of sodium have been depleted, or whose rates of glomerular filtration are severely impaired, and emphasizes the dependence of the excretion of water upon the excretion of solutes and, particularly, sodium.[30]

Concentrating Mechanism.—The foregoing discussion concerned circumstances of bodily overhydration; in the absence of such hydration, when excretion of water is curtailed, it is apparent that the free water liberated by the distal reabsorption of solutes must also have been reabsorbed. Under conditions of dehydration or under the influence of ADH, an additional amount of water must also be removed in order to render the urine hypertonic. Thus, from an isotonic filtrate, to produce a dilute urine, there is active reabsorption of solute without water; to elaborate a hypertonic urine, there must be abstraction of water without solute. When a person undergoing maximal water diuresis is given vasopressin in doses sufficient to concentrate the urine to a maximum, there occurs no significant change in the rate of excretion of sodium. If urinary excretion reflects tubular reabsorption, this indicates that, provided the amount filtered at the glomerulus is unchanged, regardless of the concentration of the urine, the rate of sodium reabsorption may be virtually constant. Since the reabsorption of this ion largely determines dilution of the urine, and since this reabsorption may be unaffected during antidiuresis, a logical query concerns the relationship, functional and anatomical, between the diluting and concentrating operations. Does the reabsorption of water without solute ($T^c_{H_2O}$) take place through a segment of tubular epithelium, which in the absence of ADH is almost completely impermeable to water yet so constituted that in the presence of this hormone it not only becomes permeable but is capable of promoting the movement of water against a considerable osmotic gradient? While conceding the possibility of such versatility, Smith considers it improbable and prefers to locate the concentrating site elsewhere in the nephron, functionally and anatomically discrete from the diluting segment, probably in the collecting ducts.[2,3] Smith indicates that on clinical grounds one can suspect such independence: Loss of concentrating ability considerably antecedes loss of capacity for water diuresis in the progress of chronic renal disease, and in the recovery phase of acute renal insufficiency the concentrating power is generally the last function to return.[3] Experimental support of a more direct nature for this separation comes from recent micropuncture studies of the rat kidney. Wirz[23] has successfully obtained fluid from the distal, as well as the proximal, tubule. The earlier finding by Walker et al.[14] that proximal fluid is isotonic with plasma has been confirmed; this isotonicity obtains both during water diuresis and dehydration antidiuresis. In the first half of the distal tubule, however, the fluid is invariably *hypotonic*, regardless of the ultimate concentration of the bladder urine. During water diuresis, this hypotonicity is maintained or increased along the course of the tubule. During antidiuresis, the fluid does become more concentrated, attaining isotonicity roughly by the middle of the tubule, and *never exceeds* isotonicity. Since bladder or ureteral urine examined simultaneously was considerably hypertonic to the plasma, this ultimate concentration must have been effected by abstraction of water, either without or in considerable excess of solute further along the nephron, presumably in the collecting system. Wirz's observations have been confirmed recently by Gottschalk,[31,32] and together with Walker's earlier findings (see footnote referring to Walker et al.[14]) afford rather solid support for the thesis that concentration and dilution are func-

tions of anatomically discrete loci within the nephron.

As a corollary to its anatomic independence, Smith postulated that removal of solute-free water, $T^c_{H_2O}$, might be a continuous autonomous process, ungoverned by ADH and capable of being carried out in the complete absence of this hormone.[2,3,5] An early hint of this possibility stems from Shannon's observation that dogs with experimentally produced diabetes insipidus, in whom a lowered rate of glomerular filtration resulted from dehydration, were able to excrete a hypertonic urine.[33] A possible contribution of a small amount of residual ADH activity could not be ruled out with certainty, since it is almost impossible to establish beyond cavil that diabetes insipidus, experimental or clinical, is ever 100% complete. Berliner and Davidson,[34] however, have recently demonstrated rather elegantly that a urine more concentrated than the plasma can indeed be formed without evidence of any activity of ADH. Dogs undergoing water diuresis ("physiological diabetes insipidus") were so prepared as to enable separate collections of urine from each kidney. After the establishment of a steady flow of dilute urine from both sides, a unilateral reduction in GFR was produced by means of a clamp applied to one renal artery. This resulted in a marked reduction in the rate of excretion of both water and solute from the clamped kidney, but the urine which was excreted was definitely hypertonic to the plasma. The urine from the unclamped kidney remained at approximately the same level of dilution, indicating that no ADH was released from the neurohypophysis during the procedure. This excretion of hypertonic urine in the absence of ADH can be explained by postulating the delivery to the $T^c_{H_2O}$ site of a small volume of, in this instance, hypotonic fluid from which the abstraction of a small quantity of water without solute was sufficient to concentrate the urine to a level above the plasma. It should be pointed out that, in these experiments, although the urine was indeed hypertonic to plasma, concentrations in excess of 475 mOsm. per liter were never obtained and the observed tonicity was generally below 400 mOsm. per liter.[34,35] The dog is capable of elaborating a urine as concentrated as 2,000 mOsm. per liter, which would suggest that although the concentration operation conceivably can and does operate in the absence of ADH, it apparently does so with severely reduced efficiency.

Action of ADH.—The geographic isolation of the concentrating locus having been established, as well as to some extent, at least, freedom from control by ADH, the next problems concern the disposition of that fluid which enters the distal tubule before the concentrating segment is reached and the nature and site of action of the antidiuretic hormone. There being no direct observations on the action of this hormone upon the renal tubule, such information as is available derives inferentially largely from comparative physiology. The amphibian skin, which is under some control by the neurohypophysial secretions, has long been recognized as an organ concerned with the over-all water balance of the organism. By the application of certain isotopic techniques to the study of isolated surviving segments of frog skin, Koefoed-Johnsen and Ussing[36] concluded that the skin has the characteristics of a porous membrane, which, upon application of small amounts of posterior pituitary extract, behaves as if these pores had been opened up. In other words, ADH had in some manner acted to increase the diameter of the pores so as to allow enhanced flow of fluid from one side of the membrane to the other. Analogizing the functions of the kidney to that of the frog skin, the distal tubule of the former can also, not illogically, be conceived as a porous membrane. Under the influence of ADH these pores open, allowing water to diffuse out along the gradient created by the preceding outflux of sodium, until isotonicity is again established. It will be recalled that in the micropuncture studies of Wirz mentioned above, fluid issuing into

the distal tubule even under considerable influence of ADH was always hypotonic; this is due to the reabsorption of sodium, leaving behind osmotically free water which is restrained from following through a virtually waterproof membrane. Under the influence of ADH, the waterproofing is in a sense removed, and the free water permitted to diffuse out passively along its gradient. Distal and proximal processes are basically similar, insofar as the reabsorption of water is concerned; in both, the movement of water follows passively upon the movement of sodium, and so the net effect is isosmotic reduction in volume of the parent filtrate. The major difference, of course, is that the proximal operations occur via a water-permeable epithelium and are totally independent of ADH and the movement of water is "obligatory"; distally, sodium transport is through a water-impermeable layer and is not accompanied by isosmotic movement of water unless ADH is present to alter the permeability of the tubular epithelium. Production of hypertonic urine, then, may be conceived as occurring in two phases. The first, which can be considered an "isosmotic making" phase[37] is the passive diffusion of osmotically free water liberated by the active reabsorption of sodium. This is under the direct control of ADH and serves to reduce the volume of fluid in the distal tubule, as well as to raise its concentration to that of plasma. The second phase, the "hyperosmotic making" process,[38] or $T^c_{H_2O}$, is the further reabsorption of an additional amount of pure water from this residual of isotonic fluid, rendering the tubular contents hypertonic to plasma.

It is apparent that the movement of water during this latter operation must take place against an osmotic gradient: water is transported from an area of solute concentration, or low water activity, to an area of isotonicity, or relatively high water content. $T^c_{H_2O}$, as regarded by Smith and Wesson and Anslow, must be an active process and, like most other processes involving active transport, seems to be subject to certain limitations. In man, the highest urinary concentration that can be achieved is about 1,400 mOsm. per liter, or a U/P ratio of between 4 and 5. In other words, there is an apparent limiting gradient against which water can be transported in only such amounts as to render the urine 4 to 5 times as concentrated as the plasma. Certain other animals can elaborate much more highly concentrated urine, some sort of record being held by the kangaroo rat, a desert animal, which can achieve a urine osmolality as great as 5,700 mOsm. per liter.[1] It has also been suggested that in addition to a maximal gradient, the amount of water yielded to the concentrating operation is limited by a maximal rate, which ordinarily does not exceed 5 to 7 ml. per minute. This figure derives from observations made during the increasing urine flow of osmotic diuresis induced under the influence of vasopressin during states of hydropenia. When urine flow exceeds a critical level of 5 to 7 ml. per minute, the calculated value for $T^c_{H_2O}$ becomes roughly constant and apparently maximal ($Tm^c_{H_2O}$). Put another way, when urine flow is large, the concentrating operation consists of a constant reabsorptive process which removes water at an approximately fixed rate—$Tm^c_{H_2O}$—from the antecedent isosmotic tubular urine, so long as the volume of the latter is in excess of the value for $Tm^c_{H_2O}$. It should be emphasized that in the hydropenic person urine flows in excess of 5 ml. per minute are very unlikely to occur, except experimentally or under pathological conditions, such as extremely heavy glycosuria. Under usual circumstances of dehydration, urine flow is scanty and the load of tubular fluid delivered to the concentrating site falls far short of the saturating value. Absorption of water is here limited not by a maximal rate but rather by the maximal concentration which can be achieved, or by a limiting U/P ratio; maximal urinary concentration is generally achieved only at urine flows below 0.5 ml. per minute.

This formulation affords an explanation for a phenomenon long recognized but only poorly understood, viz., the progressive "paradoxical" dilution of the urine despite continuous maximal activity of ADH as urine flow increases in osmotic diuresis.[39-42] The dehydrated person might logically be expected to retain water avidly and to excrete urine approaching maximal osmotic U/P ratios. Yet, if such a dehydrated person, at a time when his urine is initially concentrated and scanty, be infused with a hypertonic solution which provides a solute load demanding excretion, it can be readily demonstrated that instead of being further curtailed to a still smaller amount of even more concentrated urine, the urine volume will progressively increase and its osmotic pressure will progressively fall until at very high urine flow the osmotic U/P ratio is only slightly above unity, i. e., the urine will have been diluted toward the concentration of plasma. This occurs even if large doses of vasopressin are superimposed upon existing dehydration. The crux of the explanation is, obviously, the solute load. A seemingly invariable consequence of osmotic loading with unreabsorbable solutes such as mannitol is the imposition of a limit upon the reabsorption of solutes, such as sodium, probably both distally and proximally. A diminished movement of solute from the distal tubule results in the freeing of a correspondingly small amount of water. If the action of ADH is to facilitate only isosmotic reabsorption of this free water, even maximal amounts of this hormone cannot effect concentration of the distal tubular fluid above isotonicity. Diminished reabsorption of solute and an attendant reduced reabsorption of water will result in the accession to the concentrating site of a large volume of isotonic fluid. The removal of water at this site being limited by a maximal rate, the abstraction of this constant amount of free water from larger and larger volumes of isotonic fluid will affect the final concentration less and less and the ultimate urinary concentration will approach isotonicity in an asymptotic fashion as the rate of solute excretion increases.

This perhaps can be visualized more succinctly by reference to the formulas given above:

Since osmotic diuresis involves large urine flows, we can substitute $Tm^{e}_{H_2O}$ in Equation 3, and, by rearranging, $C_{osm}=Tm^{e}_{H_2O}+V$. Substituting from Equation 1 and further rearranging yields: $\frac{U_{osm}}{P_{osm}}=1+\frac{Tm^{e}_{H_2O}}{V}$. If $Tm^{e}_{H_2O}$ remains constant, which it does by definition, and V progressively increases, it is apparent that the fraction $\frac{Tm^{e}_{H_2O}}{V}$ must become progressively smaller, and the osmotic U/P ratio consequently approaches 1 asymptotically.

It should not be construed from the foregoing discussion that ADH is of relatively minor importance in the elaboration of hypertonic urine. Welt,[43] by appropriate calculations within the above framework, has indicated how the simple presence or absence of this hormone can account for urinary concentrations of 1,400 mOsm. per liter or 50 mOsm. per liter. From the standpoint of total water economy the quantitative importance of ADH, whether or not it affects the terminal concentrating operation, is far greater with respect to promoting the excretion of an isotonic urine, that is, prevention of the excretion of a dilute urine, than with respect to the elaboration of a concentrated urine. Berliner et al.[35] have calculated that a person undergoing maximal water diuresis would excrete 20 liters in the elimination of an amount of solute that could be contained isosmotically in 2 liters. Excretion of an isotonic urine therefore affords conservation of 18 liters of water, whereas maximal concentration of this same amount of solute would further reduce urine volume to about 500 ml., or a saving of only an additional 1,500 ml. The action of the antidiuretic hormone in allowing water to be reabsorbed isosmotically in the distal tubule is clearly critical, both in the total conservation of water and in determining the ultimate concentration of the urine.

Summarizing Recapitulation of Formulation of Smith and Wesson and Anslow.—

The process of urine formation begins with filtration at the glomerulus of water and solutes, the amounts filtered being functions, in the main, of the concentration of these solutes in the plasma and of the rate of glomerular filtration. Within the water-permeable proximal tubule the parent filtrate is isosmotically reduced in bulk by a primary active transport of sodium salts and a secondary passive diffusion of water along the resultant gradient. The thin limb and loop of Henle are conceived as regions of osmotic equilibration, allowing the diffusion of water to catch up with the outflux of sodium. An isosmotic fluid is then delivered to the water-impermeable diluting segment of the distal tubule, from which further active transport of sodium takes place, leaving osmotically unobligated water behind. In the absence of ADH this water is excreted with such of the solid constituents as had not been reabsorbed, forming a dilute urine. The "free water" so eliminated (C_{H_2O}) can be considered a mirror image of distal solute reabsorption, its magnitude depending upon the amount of sodium delivered into and removed from the diluting segment. Under the influence of ADH distal sodium transfer is apparently unaffected, but epithelial permeability is so increased that water is now permitted to follow passively until isotonicity is reestablished. The filtrate, at this stage considerably reduced in volume but again isotonic, moves further along the nephron to a site, most likely in the collecting duct, where the removal of an additional amount of water without solute ($T^c_{H_2O}$) is the final step in the elaboration of a concentrated urine. This concentrating operation is to some extent independent of the action of ADH and may be a continuous process, regardless of the final urinary tonicity. At low flows it seems to be limited by a maximal gradient against which water can be actively transported (limiting U/P ratio or maximal urinary osmolality) and at higher flows (osmotic diuresis) by a maximal rate of water transfer ($Tm^c_{H_2O}$).

This now classic concept, of which many of the originally more speculative elements have been supported experimentally, enables reasonable explanations of many phenomena and provides a logical framework within which the intrinsically renal mechanisms operative in the excretion of water and solutes can be explored. Certainly the formulation of osmolal and free-water clearance and of $T^c_{H_2O}$, whatever ultimate physiologic significance they may or may not have, facilitate a meaningful quantitative description of kidney function as related to urinary concentration and dilution.

Critique of the Classic Concept

There remain, however, certain observations which neither can be explained by, nor completely reconciled with, this hypothesis. It is apparent from the discussion of osmotic diuresis under conditions of dehydration and maximal doses of vasopressin that the present thesis adequately explains a falling U/P ratio only when urine flow exceeds the value of $Tm^c_{H_2O}$. If the concentrating operation is limited solely by the two parameters of maximum rate and maximum gradient, then a maximum U/P ratio should obtain whenever urine flow falls below $Tm^c_{H_2O}$,[44] and the transition from a maximal U/P ratio should be abrupt, which it is not, rather than curvilinear, which it is, as solute load increases. Maximal U/P ratios and urine osmolalities are observed only when solute loads are minimal and urine flows do not generally exceed about 0.5 ml. per minute. During urine flows intermediate between approximately 0.5 ml. and 5 ml. per minute, this ratio falls rapidly; the slope of this "osmotic titration curve,"[45] however, is indeterminate, and U/P and $T^c_{H_2O}$ are unpredictable.

Underlying the quantitative assessment of dilution is the postulate of solute transport from a distal segment totally impermeable to water. Observations during solute loading in patients with vasopressin-resistant diabetes insipidus indicate that even in the complete absence of ADH there is some tendency for water to diffuse out

of the tubule.[29] Control observations on such patients revealed that the excretion of solute-free water (C_{H_2O}) was approximately 5% of the filtration rate, with urine osmolality ranging between 25 and 65 mOsm. per liter. Osmotic diuresis resulted in an increased urine osmolality to 175 mOsm. per liter, while C_{H_2O} attained a maximum of 12% of the GFR; thus, the most dilute urine was associated with the lowest rate of free-water clearance and the most concentrated with the highest rate. Although the increased clearance of water can be explained by an accelerated distal reabsorption of osmotically active solute, liberating more "free" water, this would not seem likely when the loading solute is a nonreabsorbable substance, such as mannitol, whose presence is generally conceded as imposing a limitation upon the outflux of sodium. An equally reasonable assumption is that the water liberated by such sodium as was reabsorbed was prevented from following through a membrane *partially* permeable to water by the osmotic restraint exerted intraluminally by the nonreabsorbed solute. In other words, even through a membrane whose permeability to water is apparently incapable of being affected by ADH some diffusion of water occurs. This process, normally inapparent, is "unmasked" by an increase in intraluminal osmotic activity, which holds this water in the tubule. Following upon the demonstration that, in the normal person, distal permeability to water varies in a graded fashion with the dosage of vasopressin,[46] Orloff, Wagner, and Davidson[47] infused this hormone in submaximal amounts (0.5-4.0 milliunits per kilogram per hour) for prolonged periods into dogs who were undergoing solute diuresis while release of endogenous ADH was suppressed by sustained water loading. At these low dosages of vasopressin, hypertonicity did not occur except with amounts greater than 1.5 milliunits per kilogram per hour, and then only at lower rates of solute excretion: when solute excretion increased, hypotonicity supervened and free-water clearance increased despite maintenance of the same rate of hormone administration. From these observations the authors suggest that (1) permeability to water is probably never completely absent and that even during water diuresis outward diffusion of water depends upon the solute load insofar as intraluminal osmotic pressure is affected and (2) vasopressin and solute load exert antagonistic effects, the former enhancing and the latter opposing transepithelial outflow of water. Consequently, the degree of permeability afforded by a given amount of ADH may be sufficient to result in an isotonic distal tubular fluid when the solute load is low but inadequate in the presence of large osmotic loads. A concentrated urine may result from the removal of pure water from a variably hypotonic or isotonic distal fluid, depending on the interaction between ADH and intratubular osmotic pressure, and need not require the delivery to the concentrating site of an invariably isotonic filtrate, as postulated by Smith, Wesson, and Anslow. As a practical consequence it cannot be overstressed that when attempting to evaluate the concentrating potential of the kidney by whatever clinical procedure (overnight dehydration, Hickey-Hare test, administration of vasopressin, etc.) the rate of excretion of solute must be taken into consideration; it is not enough merely to observe changes in the flow and tonicity of the urine.

The perhaps seductive reasonableness of imposing a limit on the rate of $T^c_{H_2O}$ is apparent. However, evidence for the existence of any fixed or stable maximum abstraction of water is at best equivocal. $T^c_{H_2O}$ derives mathematically from the difference in magnitude between the osmolal clearance, C_{osm}, and the observed minute urine flow, V. The former, it will be recalled, is a calculated or theoretical urine volume which, at any rate of solute excretion, has a U/P of one, i. e., it is isosmotic. Plotting graphically the regression of C_{osm} on V where $C_{osm}=V$, therefore, yields a line with a slope of 1.0. Similar representation of the regression of C_{osm} versus *ob-*

served V, at flows sufficiently great to invoke $Tm^{c}_{H_2O}$, if this latter value is truly fixed at a ceiling, should result in a line parallel to that where C_{osm} equals V; that is, the slope should also equal 1.0. In point of fact, however, the data of Zak, Brun, and Smith[42] and of Boyarsky and Smith,[45] while demonstrating the linear nature of such a plot and an average slope of close to 1.0 when a number of subjects are considered, reveal the slope in any individual experiment to range between 0.8 and 1.3. Although other explanations are possible,[44] one obvious interpretation of this deviation from what theory predicts is that $T^{c}_{H_2O}$ is not constant and that, strictly speaking, $Tm^{c}_{H_2O}$ does not exist.

Movement of Water Against Osmotic Gradients.—These and other problems, while to some extent disturbing and demanding of further work, do not by any means invalidate the descriptive merits of the hypothesis. A more fundamental doubt stems from the postulate of an active transport of water against considerable osmotic gradients as the ultimate mechanism by which hypertonicity of the urine is achieved. The net movement of water between compartments can be elicited by a number of factors: (*a*) differences in hydrostatic pressure; (*b*) inequality in the number of dissolved particles per unit volume (osmotic effect); (*c*) movement with ions as water of hydration; (*d*) electrical forces acting when a membrane which contains protein or other ionizable substances separates the compartments at unequal electrical potential (electro-osmosis); (*e*) pumping of water by a contractile mechanism.[48] Osmotic and hydrostatic factors are without much question responsible for the overwhelming bulk of intercompartmental shifts of water within the organism. Such movement of water is not, in the strictest sense, active; indeed, it is necessary to invoke active transport of water as such only when differences in osmotic pressure are maintained in the absence of hydrostatic or other physical explanation.[49] Little can be said about any role of hydrated ions in water transport, since, in addition to there being little evidence for this mechanism, it could bring about only an insignificant movement: As many as 500 molecules of water can traverse frog skin in the same time as one molecule of sodium.[48] Where movement of water is associated with transfer of sodium chloride, this may be due to a "drag effect" created by flow of electrolyte through narrow pores or to other factors rendering the active transport of sodium ions inseparable from a certain concomitant movement of water.[36] Net water movement of some magnitude is theoretically conceivable by means of electro-osmotic flow, or by thermo-osmosis.[50] While such mechanisms have been invoked with respect to exchanges of water in biological systems, they have not yet received much attention; considerably more information about the nature and properties of the cell membrane is mandatory before such admittedly intriguing possibilities can be definitely applied as operational mechanisms underlying observed phenomena. Osmoregulation by means of water "pumps" characterizes certain fresh- and brackish-water protozoa which expel what certainly must be extremely hypotonic solutions by means of contractile vacuoles thus maintaining their internal osmolality above that of their hypotonic environment.[51,52] Robinson,[49,53] arguing from the premise that the intracellular milieu is hypertonic to the extracellular fluids, has proposed analogous pumping processes in mammalian tissues; neither the premise nor the analogy has been generally accepted, although, as will be discussed below, cellular hypertonicity within the kidney may well exist. Rather appealing, perhaps, is the postulate of an "osmotic diffusion pump"[54] which visualizes the movement of water across a steep transcellular osmotic gradient via an osmotically active substance which cannot escape from the cell present in high concentration at one end, attracting water from a dilute external solution. This substance can be regarded as a "carrier" which transports water across the interior of the cell. At the opposite pole, this "carrier" poly-

merizes or undergoes some other reversible change which inactivates it osmotically. Water can diffuse out as a consequence of the sudden reduction of osmotic pressure, and the "carrier" presumably migrates back to the other end of the cell, to be depolymerized or otherwise osmotically reactivated. Brodsky and his colleagues [55] have considered the energetics involved in such a process and calculated that the water-absorbing cells of the nephron would have to dissipate energy at a rate at least 1,000 times greater than that of any known living cell. Such thermodynamic considerations render this theory rather unlikely.

The purpose of the above is not to explore possible mechanisms involved with internal exchanges of water; these have been extensively reviewed elsewhere.[48-50, 53,56-58] It is intended, on the contrary, to emphasize the difficulties encountered in attempting to postulate an active transport of water as such:

> . . . alternative explanations based primarily on solute transport are available in each instance cited in support of the concept of water transport . . . (with respect to) the problem of removing water to produce hypertonic urine it is clear that it would be desirable to seek an explanation in which the primary process is one of solute transport, not requiring the movement of water against osmotic gradients.[48]

Smith was deliberately vague about the specifics of the concentrating mechanism. His views, tentatively proferred, and only "enticing as a speculation," [59] stemmed from observations about which he expressed much skepticism. From the analysis of cores of tissue cut from the short axis (cortex to papilla) of the rabbit kidney, Ljungberg [60] noted an increasing concentration of chloride from cortex through medulla to papilla. Histochemical staining of parallel sections with a silver reagent indicated the presence of chloride to be particularly heavy within the cells of the collecting tubules. While expressing certain doubts about the specificity of this technique for demonstrating intracellular chloride, Smith proposed that if the cells did indeed contain such high concentrations of an osmotically active substance, water, by means of simple diffusion in response to an osmotic gradient, would be withdrawn from the lumen into the cell, resulting in a hypertonic urine. This theory, reminiscent of the "osmotic diffusion pump" discussed above, does not solve the fundamental problem of how the water, once in the cell, would ultimately be disposed of.

Osmotic Gradients Within the Kidney.—Implicit in the hypothesis of Smith, Wesson, and Anslow is the assumption that, with the possible exception of the cells of the collecting tubules, all the medullary constituents (Henle's loops, vasa recta, interstitial fluid) are maintained isosmotic with plasma at a time when the fluid within the collecting duct is being rendered hypertonic. However, the transfer of pure water from the collecting tubule into this isosmotic region should result in some degree of dilution of the medullary interstitium and of the blood in the peritubular capillaries. Presumably, the vasa recta serve to take up this water and to carry it off for ultimate redistribution within total body water. Little is known of the rate and volume of blood flow within these vessels; if, however, these are large relative to the transfer of water out of the tubules, it is conceivable that interstitial and intracapillary osmotic pressure would not be measurably lowered. Isotonicity might be roughly maintained but under no circumstances should hypertonicity be expected. Irreconcilable within the framework established by Smith and Wesson and Anslow is the demonstration that during elaboration of concentrated urine the medullary contents are very hypertonic to plasma. Wirz, Hargitay, and Kuhn [61] removed and immediately froze kidneys from living, dehydrated rats who were forming hypertonic urine. Sections of the kidney, cut perpendicular to the medullary axis, were examined under a polarizing microscope, a technique enabling identification of individual tubules. Under careful temperature control, melting points, an index of osmotic activity of the frozen tubular fluids, were determined at various

cross sectional levels. It was found that fluid in the cortical tubules, distal as well as proximal, was always isotonic with blood, while beginning at the corticomedullary junction a progressive, roughly linear increase in osmotic pressure was developed: the deeper the section, the higher the concentration, reaching a peak at the papillary tip, generally between four and five times, but occasionally as much as eight times the concentration of the plasma. Furthermore, within any given cross sectional plane, contents of all tubular structures exhibited the same osmotic activity: at any depth below the cortex, the fluid in both limbs of Henle's loops was isotonic with the contents of the neighboring collecting duct.‖ Wirz [63] gave additional weight to these findings by demonstrating that not only is the blood within the capillaries on the surface of the renal papilla of the golden hamster not isotonic, but at the very tip of the papilla it has an osmotic pressure equal to or very slightly greater than the concentrated urine being formed at the same time. Histologically, the papilla of this animal contains primarily collecting ducts along with a few thin limbs of Henle's loops, in addition to the blood vessels. The tubular structures, being well below the surface of the papilla, are difficult to puncture with the micropipette; the vasa recta, however, some of which are easily accessible on the papillary surface, having the characteristics of true capillaries, should offer no barrier to osmotic equilibration with the medullary interstitium. An almost inescapable conclusion is that the tip of the papilla constitutes a hypertonic milieu incorporating the contents of tubules, capillaries, and interstitium. Establishment of osmotic stratification involving all renal elements from inner medulla through the tip of the papilla denotes that hypertonic urine can be formed in the absence of steep osmotic gradients across unicellular membranes.

The stratification of osmotic pressure is supported by another series of important investigations. Ullrich, Drenchkhahn, and Jarausch [64] determined the concentration of a salt solution at which osmotic equilibration obtains with whole-tissue slices taken from various levels of the concentrating kidney of the dog. The osmotic profile of whole tissue paralleled that obtained by Wirz for tubular fluid: isotonicity with blood in the cortex and a steady increase in osmotic pressure from corticomedullary boundary to papilla. Of particular importance is the recognition that the osmotic behavior of a slice of tissue reflects shrinkage or swelling of the cells themselves; the intracellular compartment must, therefore, be involved in the process of osmotic stratification. The last slice, taken from the papillary tip, had an osmotic activity virtually identical with that of the urine passed by the animal shortly before the kidney was examined. Since an increasing percentage of the cross sectional area of the medulla is progressively occupied by the collecting ducts as the papilla is approached, it is apparent that osmotic equilibrium must obtain between the ductile epithelium and the intraluminal urine. These experiments of Ullrich and Wirz indicate that the final concentrating operation does occur within the collecting duct but need not involve an active secretion of water. By virtue of osmotic stratification, the collecting tubules, as they traverse the medulla, pass through *and equilibrate with* a milieu of increasing hypertonicity: this system offers the obvi-

‖ These experiments have been criticized on the grounds that the results obtained cryoscopically might have been influenced by changes in diffusion occurring post mortem and during the processes of freezing and melting.[65,66] Small differences in osmotic pressure between adjacent tubules might not be recognized by this technique, inasmuch as the hypotonicity in the early distal tubule, evident by direct micropuncture, was not revealed by direct cryoscopy. Wirz [62] does point out, however, that the freezing-point depression within the papilla of the concentrating kidney of the rat is greater than 4 C (approximately 2,200 mOsm. per liter), a value approaching the urinary osmotic ceiling of the rat. To regard this as an average papillary osmotic pressure would require the contents of the collecting tubule to be much more hypertonic than this in order to effect such a large rise in osmotic pressure in the isotonic contents of the loops, blood vessels, and interstitium.

ous thermodynamic advantage of allowing water to exist passively down its gradient from the dilute intraluminal area of high water activity to the relatively concentrated region of low water activity provided by the whole of the medullary contents.

The Countercurrent Hypothesis

The mechanism proposed whereby an osmotic stratification is established within the kidney presents a provocative and challenging exercise in physiologic speculation. Hargitay and Kuhn,[65] imputing major functional significance to the peculiar anatomic configurations of the renal elements, in contrast to the "linear" view inherent in the more classic approach, introduced into renal physiology the unique concept of a "hairpin counter current multiplier system."

The general principle of counter current flow is well recognized. In industry, for example, it is utilized in regenerative heat exchangers where the hot air of the exhaust preheats the cold air of the intake, resulting in the conservation of heat within the system by preventing significant losses to the outside. This principle, in one of its simplest applications, can be exemplified by visualizing a jacketed tube, such as a simple laboratory distillation apparatus. Hot air enters the top of the tube, and cold air is introduced into the bottom of the jacket; the direction of air flow in the jacket is opposite to that in the tube, hence the term "countercurrent." Heat, obeying the laws of diffusion, will move across the common wall separating the compartments into the colder inflowing air and will tend to be retained at the top of the system. The temperature towards the bottom will be only slightly increased over that of the incoming air; the result is a large gradient in temperature between the two ends of the system but only a very small difference in temperature across the tubes at any given level. Efficiency of heat exchange in a system such as outlined obviously depends upon the rate of flow of air: the slower the flow, the greater the time for equilibration between inflowing and outflowing currents and the more nearly identical the temperatures in the two compartments at any given distance from the ends. Conversely, at more rapid flows, the exchange of heat across the wall will be lessened, the transmural gradient will increase, more heat will escape from the system, the end-to-end gradient will diminish, and heat conservation will be correspondingly limited.

Many examples of countercurrent devices, designed to conserve heat or oxygen, occur in nature. Somewhat analogous to the example given above and a model of surpassing natural ingenuity is the heat-conserving machinery of the whale.[66] This warm-blooded homeothermic mammal, cavorting comfortably in arctic seas, must somehow prevent loss of body heat from the expansive surface of extensively vascularized fins, flippers, and flukes. The vascular supply to these structures is so arranged that the major arteries carrying warm blood from the heart are centrally suspended within a ring of cooler-blooded thin-walled veins, the concentric conduits serving as a countercurrent heat exchanger which prevents the dissipation of heat peripherally and allows its conservation centrally, within the bulk of the whale's body. The conservational properties of countercurrent flow need not be restricted to concentric systems. Two tubes lying adjacent, heat entering the end of one and flowing counter in direction to the cooler contents entering the opposite end of the other, would serve similarly to retain heat towards its point of entry. The presence of venae comitantes accompanying the major peripheral arteries led Bazett et al.[67] to apply this general principle of heat exchange to man. Such a rudimentary and most likely vestigial counter current system probably plays a minimal role in over-all heat regulation, although the arrangement of the pampiniform plexus of veins around the internal spermatic artery, by acting as a countercurrent exchanger, may aid in the maintenance within the scrotum of a testicular temperature compatible with spermatogene-

sis.[68] An efficient parallel arrangement of veins and arteries is found in the warm-blooded aquatic birds who stand with their feet in cold water for prolonged periods and must conserve heat or ultimately equilibrate with their cold environment. Peripheral arrangement of the vascular system as a countercurrent device provides for central retention of heat, while the feet, whose metabolic demands are fortunately low, remain cold.[69]

A specialized modification of counterflow consists of a single tube bent back upon itself so that its two limbs are in contact; continuity of flow is maintained by the bend, but flow within the two limbs is now in opposite directions. The unique feature of this arrangement is that a large concentration of a given property can be maintained at the bend and not be dissipated by being carried away via the outgoing stream. Quantitative illustrations of this "hairpin counterflow" have been given in some detail by Scholander.[70] An application of this in nature occurs in association with gas secretion by the so-called "red gland" found in the swim bladder of certain deep sea fishes. The blood supply to this gland is the rete mirabile, a unique vascular structure consisting of closely intermingling parallel capillaries whose afferent and efferent branches are connected via a small hairpin bend. In cross section, the rete resembles a checkerboard wherein black squares (afferent limbs) always border white (efferent limbs) and vice versa; this geometrical arrangement affords maximal diffusion between the two limbs. In the rete mirabile this agglomeration of capillaries serves as a very efficient countercurrent diffusion exchanger which makes possible the maintenance of a steep tension gradient for oxygen (in excess of 100 atmospheres) within the swim bladder by avoiding oxygen loss via outgoing blood. A fuller treatment of the entire subject of countercurrent flow as it occurs in nature is given in a delightful review by Scholander.[69]

Application of all this to the kidney stems from the anatomical orientation of the structures within the medulla. This unique spatial configuration provides a virtual battery of countercurrent systems arranged in parallel. The ascending and descending limbs of the loops of Henle constitute one such system, and the arterial (descending) and venous (ascending) limbs of the vasa recta, intermingling with and parallel to the loops of Henle, form another. The active role in creating a high osmotic pressure at the papilla is assigned by Hargitay, and Kuhn and by Wirz to the loop of Henle. An explanation of this theory has been presented in detail elsewhere[65,71] and will only be summarized here. The entire operation is based on the presence of a longish tube that bends back on itself, so that flow in the two limbs is opposite in direction (hairpin countercurrent), combined with some active process that creates a *small* concentration difference between the two limbs, the descending being *slightly* hypertonic relative to the ascending. The multiplier effect begins to operate when the relatively hypertonic contents of the descending limb are pushed around the hairpin bend by bulk flow: the ends of the two limbs near the bend are now in osmotic equilibrium, and the slight pressure difference between them is temporarily abolished. If the same active process continues to operate, maintaining a small osmotic gradient across the boundary between the two compartments, the fluid in the lower portion of the descending limb then becomes even more hypertonic than it was at the beginning. This still more concentrated solution once again flows around the bend, and at the lower end of the system the two limbs reequilibrate at an osmotic pressure higher than that which initially obtained. Continuous action of such a mechanism will ultimately result in a steady state: fluid within the entire system will become progressively more concentrated toward the bend, resulting in an osmotic stratification along the long axis of Henle's loop, whereas the concentration difference between the limbs, at any given level, will be no greater than that created by the initiating active

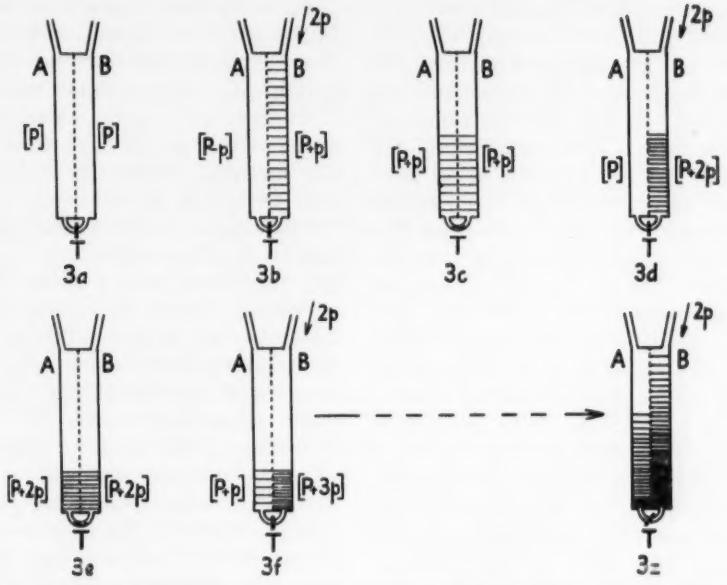

Illustration of the hairpin countercurrent multiplication theory. Two long, narrow tubes, *A* and *B*, separated by a semipermeable membrane, are connected at the bend by opening a tap, *T*, allowing fluid to flow from *B* into *A*. Initially both compartments are in equilibrium at osmotic pressure *P*. With the tap closed, an active mechanism transports solute at concentration p, small in comparison with *P*, from Tube *A* into Tube *B*. The osmotic pressures are now $P-p$ and $P+p$ in *A* and *B*, respectively, a difference of $2p$, which is maintained across the membrane by the active process (*3b*). If the tap is opened to allow one-half of the contents of *B* to flow into *A*, equilibrium will obtain in the lower halves of both compartments at a pressure of $P+p$ (*3c*). If the same active process, p, continues to act, with the tap closed, solute will be transported from left to right until the osmotic pressure is *P* in the lower half of Tube *A* and $P+2p$ in the lower half of Tube *B* (*3d*). If the tap is again opened until one-quarter of the fluid in *B* has passed into *A*, the contents within the lower quarter of the two compartments will again have the same osmotic pressure, $P+2p$ (*3e*). If the active process, p, continues, solute will again traverse the lower quarter of the membrane from left to right, until the concentrations in the lower quarter of the two compartments become $P+p$ and $P+3p$ (*3f*), the difference between them maintained at $2p$ by the active process. If instead of conducting this imaginary experiment in discrete steps, the tap *T* is left slightly open at all times, there is a slow flow of fluid down Tube *B* and up Tube *A*, while the osmotic difference, $2p$, is maintained across the membrane by continuous action of the active transporting mechanism. A steady state finally is established in which solute is progressively more concentrated at the lower ends of the system (*3z*). The difference in osmotic pressure between the top and bottom of the two compartments may be much larger than the difference, $2p$, between the two sides of the membrane at any level. (Reproduced with permission from Robinson, J. R.: Reflections on Renal Function, Springfield, Ill., Charles C Thomas, Publisher, 1954.)

process. This is illustrated in more detail in the Figure.[72]

Translating this to the osmotic relationships that might obtain within the kidney, one can assume that some active mechanism removes a relatively small amount of solute, amounting to, for example, 75 mOsm. per liter, from some site in the outer medullary portion of the ascending limb of Henle's loop and transports it into the corresponding level of the descending limb. The respective osmotic pressures within these limbs, formerly in equilibrium at 300 mOsm. per liter, are now 225 mOsm. per liter and 375 mOsm. per liter; i. e., a difference of 150 mOsm. per liter, which is constantly maintained by this active mechanism. The processes of flow and equilibration as outlined above continue until a steady state obtains, at which time the osmolality at the

lower end of the descending limb and within the bend is 1,200 mOsm. per liter. At the lower end of the ascending limb, just above the bend, the concentration would be 1,050 mOsm. per liter; in the middle of the system the concentrations might be 650 and 500 mOsm. per liter, and at the point of origin, osmotic pressures would be unchanged, i. e., 375 and 225 mOsm. per liter for the descending and ascending branches, respectively. The net effect is a stratified increase in osmolality from 300 mOsm. per liter at the corticomedullary boundary to 1,200 mOsm. per liter at the papillary tip, or an increase in the stem-to-stern gradient of 900 mOsm. per liter. The single effect of the initiating active process, amounting to only 150 mOsm. per liter, is maintained between the limbs, but, by virtue of hairpin flow, was *multiplied* six times within the long axis.

It is not necessary to restrict these operations to the limbs of the same loop. If solute is removed from one ascending limb, it can be taken up by any of the descending limbs which happen to lie adjacent; the result would not be altered.

This ingenious scheme explains almost everything connected with the elaboration of a hypertonic urine. The contents of the proximal tubules, contained exclusively within the cortex, are at all times in osmotic equilibrium with the plasma. During its traversal of the descending limb of Henle's loop, this initially isosmotic fluid becomes progressively more concentrated as it approaches the hairpin bend. During the return along the ascending limb, the fluid is rediluted, and within the distal convolutions, back in the cortex, there is once again an isosmotic fluid, which is presented in turn to the collecting ducts. From the collecting ducts, which pass through the hypertonic environment generated by events in Henle's loops, water is given up passively to its concentrated surroundings; the ducts do not bend back to the cortex, and this urinary concentration is final. Removal of water to concentrate the urine ($T^c_{H_2O}$) is indeed the final operation and occurs beyond the confines of the nephron proper. In this sense, the theories of Smith and of Wirz, Hargitay, and Kuhn are in complete accord; the disagreement concerns the mechanism by which the water is removed and in the role played by the loop of Henle. The weight of present-day evidence would seem to lie with the latter.

The paradox concerning the relationships between urinary concentration and solute load when vasopressin is administered during osmotic diuresis is to some extent resolved by this thesis. The limit to which the urine in the collecting tubule can be concentrated depends directly upon the osmotic concentration within the medullary interstitium. The latter, in turn, depends upon the efficiency with which water is removed in order to maintain this hypertonicity. Osmotic diuresis provokes the delivery to the collecting ducts of a progressively increasing volume of isosmotic filtrate, from which, under the influence of vasopressin or ADH, a correspondingly large volume of free-water is removed into the interstitium in the attempt to concentrate this filtrate. As the capacity to remove water from the interstitium becomes progressively limited by the accession thereto of more and more free water, the interstices will become increasingly more dilute and the gradient across the epithelium of the collecting system will gradually diminish so that isotonicity with plasma will be approached asymptotically. The curve relating urine flow to urine concentration is therefore curvilinear, without abrupt break, and a true maximum for $T^c_{H_2O}$ will not be achieved.

Critique of the Countercurrent Hypothesis

As with any unitary theory, difficulties and shortcomings abound. One of these is obvious: Blood, as well as tubular fluid, presumably tends to equilibrate with the increasing tonicity in the medulla. This conjures up a vision, in Robinson's words,[73] "of red blood corpuscles opening and closing like concertinas" as they flow from

isotonic to hypertonic to isotonic regions. There are several ways of getting around this. It is possible that the time it takes to traverse the medullary circuit may be quite rapid, and the erythrocyte would not be in contact with hypertonic surroundings long enough to become crenated. Alternatively, if crenation does occur, it may, contrary to general belief, be reversible if the duration of this state is not too long. Relevant data concerning either of these possibilities are not readily available. Another alternative is that the fluid perfusing the vasa recta may consist largely of plasma and thus be essentially free of significant numbers of red cells. This idea stems from the theory of plasma-skimming and cell separation proposed by Pappenheimer and Kinter,[74-76] according to which the juxtamedullary circulation may offer a preferential "short-circuit" for red cells; by virtue of laminar flow, plasma would be skimmed off into the medullary peritubular capillaries, which would consequently be perfused by blood of very low hematocrit. The recent report by Lilienfield, Lassen, and Rose[77] that, compared with the rest of the kidney, the renal papilla is strikingly devoid of erythrocytes, grants this premise some plausibility.

A somewhat more difficult problem concerns the nature of the active process which actually initiates the stratifying activities of the countercurrent system. In their much misunderstood original model, Hargitay and Kuhn[65] used a small head of hydrostatic pressure. This was utilized because it was a simple single effect which could be measured directly, and was not meant to indicate that changes in hydrostatic pressure necessarily operate within the kidney. They well might, but with urinary osmotic pressures in some mammals well in excess of seventy atmospheres (2,800 mOsm. per liter), in view of hydrostatic pressures actually observed, this seems unlikely even with the multiplying effect of hairpin counterflow.[71] In their earlier publications, Wirz and Hargitay, and Kuhn[61,65,71] suggested that the initial step might be an active transport of water across the interstitium, from descending to ascending limb, or a movement of solute in the opposite direction. This thesis was based upon the aforementioned model of Hargitay and Kuhn,[65] which consisted solely of tubes separated by semipermeable membranes and included no interstices: The water yielded by the collecting tubule was represented as taken up by the limbs of Henle's loop. This initial hypothesis has been recently challenged by Berliner, Levinsky, Davidson, and Eden.[35] These authors indicate an apparent "internal contradiction which . . . seems insurmountable," namely, that to be effective hypertonically (in removing water from the environment) the loop of Henle must be permeable to water, but in order that a high osmotic concentration within the loop be established by means of sodium transport from one limb to another, the loop must be water-impermeable.[35] This criticism is valid insofar as it applies to the mechanism as originally envisioned by Wirz, Hargitay, and Kuhn[61]; however, a more recent formulation by Wirz[62] would seem to contain no such contradictions. In essence, he proposes that as an initial step in concentrating the urine sodium, with a balancing anion such as chloride, is actively extruded from the thick portion of the ascending limb of Henle's loop ¶ into the surrounding interstitium, rendering the latter slightly hypertonic. In response to this hypertonicity, water moves out of the descending limb, thereby concentrating slightly the residual contents within this segment. The fluid, now slightly more con-

¶ There is some difference in terminology regarding the anatomical divisions of the nephron as commonly considered from that used by Wirz.[62] The distal tubule is generally conceived as beginning at the end of the thin limb and extending to the collecting tubule. Wirz regards the distal segment as originating where the thick ascending portion of the loop of Henle returns to the cortex and touches its own glomerulus. The latter definition has the simplifying advantage of restricting this segment to the convoluted portion which resides entirely within the cortex.

centrated than that in the ascending branch, is pushed around the bend by bulk flow and the countercurrent multiplication operation begins. Wirz further posits that the descending limb is influenced by ADH; such action would increase the permeability to water so that equilibration with hypertonic surroundings may proceed more efficiently and initiate the multiplying effect more quickly. Differential permeability of the two limbs of Henle's loop is thus attained under the influence of ADH, the descending being selectively rendered more permeable than the ascending. As for the water transferred into the interstitium from the collecting ducts during the concentrating process, Wirz [78] indicates that the blood in the capillaries, rather than the loop of Henle, serves to carry this away; the interplay between hydrostatic and colloid osmotic effects in governing transcapillary exchange of fluid presumably being the same within the kidney as it is throughout the body in general.

Role of Active Transport of Sodium.—Evidence for the primacy of sodium transport in this scheme of operations comes from several sources and seems well founded. The micropuncture studies of Wirz [23] referred to earlier, indicate hypotonicity within the early part of the distal tubule whether the urine is hyper- or hypo-osmotic. The bulk of osmotic activity within the tubule being due to sodium and its anions, it is reasonable to conclude that distal hypotonicity is a reflection of prior removal of these salts; a logical site for such removal is the thick ascending limb of Henle's loop. Similar micropuncture studies by Gottschalk [31] in rats undergoing osmotic diuresis with several different substances reveal that early distal fluid is most hypotonic when sodium chloride is employed as the loading solute, suggesting that whatever the circumstances of solute excretion hypotonicity within the distal segment is due primarily to prior reabsorption of sodium salts. Ullrich and Jarausch [79] performed chemical analyses of whole tissue slices taken from kidneys of dogs who were excreting concentrated urine and found a graded increase in the tissue levels of sodium and chloride, extending from outer medulla to papilla. Their findings are reminiscent of those of Ljungberg,[60] who found a similar situation with respect to chloride in the rabbit kidney (see above). Taken in toto, this is an impressive supporting basis for the postulate of a critical role for sodium (chloride) in the concentrating mechanism of the kidney.

Functions of Henle's Loop and Vasa Recta.—In a previous presentation,[71] as well as in the more recent formulation,[62] Wirz recognizes the hairpin configuration of the vasa recta, and indicates that the blood therein "may adapt itself to the osmotic pressure of the surroundings by a passive uptake (on its way down) and release (on its way up) of osmotically active solutes." [62] While perhaps not explicitly stated, this describes the function of the peritubular capillaries as a countercurrent exchanger serving to maintain the hypertonic environment engendered by the multiplying action of the loop of Henle. Predicated largely on the inadequacies of the original Wirz hypothesis, Berliner and coworkers [35] have evolved an alternative proposal, in which the mechanism as proposed by Wirz is modified so that more emphasis is placed upon this action of the vasa recta. These authors regard the loop of Henle as a site from which sodium, along with a balancing anion, is transported into the interstitium in excess of water; these ions, freely diffusible through the walls of the capillaries, would be maintained at high concentration along the long axis of these vessels by virtue of hairpin counterflow. The vasa recta thus operate as a countercurrent diffusion exchanger, analogous to the rete mirabile discussed above. This hypothesis differs from that of Wirz, Hargitay, and Kuhn in invoking no multiplying action by Henle's loop, which is regarded simply as a source of sodium ions, ungoverned by ADH, and functioning continuously. Also, since Berliner et al. conceived the loop as impermeable to water,

sodium salts are pumped without an equivalent amount of water; the contents of the loop must consequently be diluted to hypotonicity, in contrast to the idea of Wirz, which demands that the fluid within the loop be quite hypertonic. The cryoscopic data of Wirz, Hargitay, and Kuhn [61] indicate that the contents of Henle's loop becomes progressively more concentrated toward the papilla; this is in accord with the hypothesis as put forth by them and argues against that of Berliner and his colleagues. While cryoscopic measurements are subject to some criticism (see footnote to section on osmotic gradients), no direct experimental evidence against them has been brought forth to date; whether the fluid within the loop of Henle is in fact hypertonic or hypotonic can be definitely ascertained only by direct analysis.#

Inherent in the nature of any countercurrent *exchanger* (as opposed to a countercurrent *multiplier*) is that such a device cannot establish a high concentration of any property *de novo*, be it heat, oxygen, or osmotic pressure. Such a system can only conserve that which already exists; it cannot create. Tissue concentration of sodium (chloride) at the tip of the papilla in the dog approaches 850 mM. per liter,[79] requiring the loop of Henle, at least at the bend, to pump sodium, from a fluid becoming progressively more hypotonic, at such a rate as to achieve these levels within the medullary interstices in order for the vasa recta to function effectively as a countercurrent exchanger. Although a not inconceivable operation, this is, in terms of work, a more extravagant demand upon the epithelium of Henle's loop than is required by the hypothesis of Wirz. This latter necessitates a transport of sodium only in such amount as to effect a concentration difference between the ascending and descending limbs, at the corticomedullary boundary, of approximately 150 mOsm. per liter *; this single small effect is subsequently multiplied by the countercurrent system within the loop so that maximum concentration automatically obtains at the bend without involving further significant osmotic work. Recognizing that solute need not of necessity be added to the capillary at the bend, Berliner et al. indicate that a qualitatively similar stratification of osmotic pressure within the medulla will obtain no matter where along the length of the capillary solute is provided.[35] These authors, however, do not propose any differentiation in rate or amount of sodium transport along the course of Henle's loop, leaving unanswered the fundamental question of how osmotic stratification does become established. Even so, addition of solute elsewhere than at the bend would perforce change the profile of the concentration gradient so that its maximum would by definition be removed from the papilla. In view of the demonstrated almost linear increase in osmotic pressure extending from outer medulla to a maximum at the papilla, this argument, insofar as it might apply to a site of sodium pumping at some distance from the papillary tip, seems irrelevant within the framework of their hypothesis; if anything, it emphasizes the critical necessity for an already established high concentration of solute at that part of the capillary closest to the papillary tip, i. e., in the pericapillary interstitium surrounding the bends of the vasa recta. The hypothesis suggested by Berliner and his associates, while embodying certain

Since this manuscript was completed Gottschalk and Mylle [91] have reported success in puncturing the bend of the thin limb of Henle's loop in the hamster. Fluid so obtained was definitely hypertonic to plasma, ranging from 453 to 1,391 mOsm. per liter, and was isosmotic with the contents of adjacent collecting ducts at the same level; fluid from cortical segments of proximal and late distal convolutions was isosmotic, and from early distal tubules, hypo-osmotic to plasma. The authors consider these findings to be highly consistent with the concept that the loop of Henle functions as a countercurrent multiplier to concentrate the urine.

* This figure derives from Figure 1 of Wirz,[88] in which the tubular fluid-plasma osmotic ratios in the early distal tubule of the concentrating rat kidney are represented as ranging between 0.5 and 0.7. At plasma osmotic pressures of 300 mOsm. per liter, assuming that only sodium chloride was removed, this implies transport of at most 75 mEq. per liter, equivalent to 150 mOsm. per liter.

attractive features, would seem to offer no advantage over that of Wirz, which is more in keeping with the experimental observations available at present.

Role of Urea.—A special role for urea in the concentrating process has been explored by Berliner et al.,[35] Schmidt-Nielsen,[20] and Klümper, Ullrich, and Hilger.[80] In the extensive chemical analyses noted above, Ullrich and Jarausch[79] found that of all the substances measured (Na, K, Cl, Mg, Ca, inorganic phosphate, urea, amino acids, and exogenous creatinine), the highest concentration gradient was achieved by urea, the concentration of which at the papilla equalled that in the urine. Tissue concentrations of urea at the papilla reached levels as high as 840 mM. per liter; maximum papillary-tissue concentrations of sodium were comparable (425 mEq. per liter, equivalent to 850 mOsm. per liter of sodium chloride).[79] Berliner et al.[35] report similar findings, but somewhat lower tissue concentrations of urea than obtain in the urine. The equally important roles of these substances in the composition of the total tissue osmolality, and hence in determining final urinary tonicity, is apparent. Urea, despite its apparently free diffusability within the organism in general, is present in urine at concentrations much higher than its plasma level, a finding which indicates relative impermeability of the nephron to this substance. Berliner et al.[35] implying that the collecting duct is peculiarly permeable to this substance, as compared with the rest of the nephron, suggest that urea diffuses out of the duct along with water and is deposited in the medullary interstitium along with the sodium already present. The urine thus contributes some of its urea to the osmotic stratification, enabling the establishment of a higher peritubular osmotic concentration than can be effected by the salts of sodium alone. The function of urea within the interstices is thus to balance to a large extent the osmotic effect of the urea within the collecting tubule, countering any restraining effect of the latter upon the outward diffusion of water; medullary urea thus would appear to have no active role in the concentrating operation as such.

An entirely different explanation has been offered by Schmidt-Nielsen,[20] who suggests that the high medullary concentration of urea is not the result of simple passive diffusion, as outlined above. This author proposes an active tubular transport of urea against a concentration gradient; this small process is in turn amplified by the multiplier effect of countercurrent flow within the medullary structures, resulting in a high interstitial, and, consequently, a high urinary concentration of this substance. While this is a rather attractive suggestion, there exists to date no definitive evidence that urea is in fact actively transported by the tubular epithelium of the human kidney.

Klümper, Ullrich, and Hilger,[80] in a series of elegant experiments involving microcatheterization of individual collecting ducts,[81] have demonstrated that the concentration of urea within the duct increases toward the papilla, although to a smaller degree than that of inulin. It being generally conceded that inulin is not reabsorbed from any portion of the nephron, the degree to which this substance is concentrated may be taken as an index of the amount of water removed to effect concentration of the urine. That urea was not concentrated to the same extent as inulin denotes that some of the urea that reached the collecting system subsequently found its way into the medullary contents through the ductile epithelium. The authors suggest that this was accomplished by a passive diffusion of urea, along with the water leaving the ducts; the possibility of an active secretion of urea cannot, however, be eliminated.

A Modification of the Countercurrent Hypothesis

The principle of countercurrent flow, first applied to the kidney in 1951, has been regrettably neglected until recently. It can, therefore, be looked upon as a "new" theory, and novelty tempts speculation. Despite

its overwhelming rationality in the main, there remains at least one major problem inherent in any countercurrent system. ADH exerts its effects immediately; yet, whether the loops of Henle function as a multiplier or as a sodium pump, it would take some time for either mechanism, as presently postulated, to establish as well as to dissipate, osmotic stratification. How, then, is rapidity in attaining a concentration gradient achieved, and what role can be assigned to ADH in this process? A clue is provided by Berliner et al.[35] in their recalculation of the data of Ullrich, Drenckhahn, and Jarausch,[64] which reveals that although the concentration of sodium in tissue water during diuresis is much lower than during antidiuresis, the total amount of sodium in the medulla may be 80% or more of that present during antidiuresis. This indicates that the solute necessary to provide the osmotic gradient along which water is withdrawn from the collecting tubules during the formation of hypertonic urine is present at all times. The problem then becomes not so much one of establishing a gradient anew, but rather one of unmasking or activating one which is readily available, presumably by the action, in some manner, of ADH. It has been proposed that the action of this hormone is to increase the permeability of the descending limb of Henle's loop[62] and of the collecting tubule,[35,47,62] so that water can diffuse out of the lumen into the relatively hypertonic medullary interstices. However, if ADH indeed acts simply to allow diffusion of water, the medullary interstitium will become progressively more dilute, and the purpose of the countercurrent system will ultimately be defeated.

Role of ADH.—This difficulty can perhaps be resolved by postulating delivery, under the influence of ADH, not only of water but of sodium salts as well into the medullary interstices. The present concept of the action of antidiuretic hormone with respect to reabsorption of water from the renal tubule is largely inferential, based on analogy with the effect of this hormone on the amphibian skin. The action of neurohypophysial hormones in stimulating active transport of sodium by the frog skin and toad bladder is well established[82-84]; it seems not at all unreasonable, therefore, to extend the analogy with these amphibian structures to include this sodium-transporting activity as well. It is difficult to envision how hypertonicity within the renal medullary and papillary tissues can obtain in the presence of reabsorption into this area of water alone, unless sufficient solute were also added to counteract the inevitable diluting effect of this water. Osmotic stratification within the long axis of Henle's loop is undoubtedly present to a greater or lesser extent at all times. The transport of sodium salts under the influence of ADH might be accomplished in such fashion as to reflect this gradient within the interstitium; by virtue of their arrangement as countercurrent exchangers, the vasa recta would maintain this stratification so that osmotic pressure would be highest at the bends. It might seem, at first glance, that transport of sodium as suggested above would result in hypotonicity of the contents of Henle's loop, thus dissipating the effects of the multiplying operation. This need not follow necessarily, however. The finding by Wirz[23] and Gottschalk[31] of hypo-osmolality in the early distal tubule during elaboration of hypertonic urine indicates that sodium is continually pumped from the ascending portion of Henle's loop which, even in the presence of ADH, remains virtually impermeable to water. The osmotic activity surrounding the descending loop in the outer medulla will, under influence of ADH, be a function of the sodium salts transported both from the thin segment and the thick ascending portion of the loop and would be even greater than that obtaining in the absence of hormone. In the presence of the increased permeability induced by ADH, and enhanced by its tendency to follow along the gradient created by sodium transport, a rather large volume of water will exit from the descending limb quite rapidly; the contents within

this segment should remain hypertonic relative to that of the ascending branch, and multiplication within the loop would continue as before. Indeed, transmural movement of a relatively large volume of fluid out of the thin limb in response to ADH would diminish considerably the rate of flow through this structure of the residual contents. Since efficiency of a countercurrent system varies inversely with the velocity of flow within it, there results a situation most favorable for the augmentation to a maximum of the gradient already present within the long axis of Henle's loop; a gradient which, when a steady state ultimately obtains under the action of ADH, would be mirrored in the interstitium, blood vessels, and, finally, the collecting tubules. The role of the loop of Henle, in this modest modification of the ideas of Wirz, Hargitay, and Kuhn and of Berliner et al. is to provide, by means of countercurrent multiplication, an established osmotic stratification which, under the influence of ADH, whose effect on sodium transport is virtually instantaneous,[84] can be rapidly reflected in the medullary interstices. By retaining the advantages afforded by the multiplication principle, the necessity for postulating hypotonicity within the loop, and hence the presence of large osmotic gradients across very thin epithelium, is largely obviated. The sodium-pumping action of the thin segment of the loop, visualized as a continuous process by Berliner et al., is here regarded as being governed directly by ADH, proceeding in its absence only to a minimal extent, if at all.

It is tempting, too, to speculate that the loop of Henle may be the only structure upon which ADH exerts its physiologic influence in the production of hypertonic urine. It is generally accepted that the major effect of this hormone is upon distal tubular epithelium, facilitating the diffusion of water so that an initially hypotonic fluid is rendered isosmotic before reaching the collecting system. As discussed earlier, the tubular epithelium is probably never completely impermeable to water. If, therefore, rate and volume of flow within the distal tubule are sufficiently meager, and osmotic restraint exerted by intraluminal solute correspondingly small, it is entirely conceivable that equilibration might result between tubular contents and the isosmotic cortical interstitium, unfacilitated by ADH, simply from the slow diffusion of water down the gradient created by prior reabsorption of osmotically active solute. Removal from Henle's loop of a large portion of the filtrate remaining after proximal reabsorption, as would occur by such a mechanism as just proposed, would create precisely these conditions within the distal tubule. Support for this idea is suggested by measurements of hydrostatic pressures within the nephron, obtained by direct micropuncture. Wirz[85] demonstrated that under the influence of vasopressin, while intraluminal pressure within the proximal tubule was not affected, that in the distal tubule fell dramatically and almost immediately to values only slightly above atmospheric pressure. Alternative explanations certainly exist, but one possible interpretation of this observation is that vasopressin evoked a sudden reduction in the volume of fluid perfusing the distal tubule, perhaps by stimulating prior removal of fluid from the loop of Henle.

Wirz[23] and Gottschalk[32] have independently shown that, in the absence of ADH, during the production of a dilute urine, fluid within the entire distal tubule remains hypotonic but is nonetheless consistently more concentrated than concurrent final urine. This led Wirz[62] to postulate an action of ADH on the collecting tubule, since, if water were to move out of this segment in the absence of such action, as proposed by Smith and Wesson, and Anslow, bladder urine should be more concentrated than distal tubular fluid. This phenomenon can be equally well explained by a reabsorption of sodium salts during diuresis in excess of water, without requiring complete water impermeability on the part of the ductile epithelium. In view of the demonstration by Hilger, Klümper, and

Ullrich [86] of considerable movement of sodium out of the collecting duct during antidiuresis, it seems not illogical to homologize the functions of this segment with those of the distal tubule, in this regard, and to assume that transport of sodium occurs independently of the final urinary concentration. Velocity of flow along the duct during antidiuresis, now very slow and scanty should offer little hinderance to outward diffusion of water through a membrane permeable in some degree simply in response to the very high transmural osmotic gradient, without necessarily invoking any action of ADH. Several authors,[34,35,47] based largely on the failure of Berliner and Davidson [34] to obtain maximally concentrated urine as a result of clamping the renal artery during water diuresis in the dog, have also argued in favor of an action of ADH on the collecting tubule. In the experiments reported by Ullrich, Drenckhahn, and Jarausch [64] osmolality of tissue slices at the papilla of dogs undergoing water diuresis ranged between 300 and approximately 450 mOsm. per liter of tissue water, corresponding to urinary concentrations of 60 to 210 mOsm. per liter; values for the osmolality of the urine excreted by the unclamped kidney in the experiments of Berliner and Davidson [34] were comparable or somewhat lower, indicating a roughly equivalent degree of diuresis in the two sets of studies. The maximal concentrations of urine obtained by Berliner and Davidson from the clamped kidney fell within the range of tissue osmotic pressure observed during diuresis in the experiments of Ullrich et al. It is, therefore, entirely possible that flow of fluid through the collecting tubule was so curtailed by virtue of marked depression of GFR consequent upon clamping of the renal artery that virtually complete equilibration between the contents of the ducts and papillary interstitium was able to occur, and the resulting urine was indeed "maximally" concentrated. In the experiments of Berliner and Davidson failure to observe urines more concentrated than 475 mOsm. per liter need not necessarily represent lack of hormonal effect upon permeability of the collecting duct to water, but rather inability of the loop of Henle, in the absence of ADH, to transport sufficient sodium and water to effect a higher interstitial concentration gradient.

Furthermore, since the thick ascending portion of Henle's loop, grossly continuous and histologically almost identical with the cortical distal tubule, is manifestly unaffected by ADH, it must be granted that if ADH acts upon the distal segment at all, its effective action is restricted to the cortical convolutions. Seven-eighths of the nephrons of the human kidney have no long thin limbs and are contained almost entirely within the cortex [87-89]; the total fluid contents within them is presumably virtually isosmotic at all times. There would seem to be little reason, therefore, to invoke action of ADH upon distal tubular permeability of cortical nephrons if the sole result of such action is indeed only to effect isotonicity within this segment. Significant effect of ADH upon the distal tubule, with respect to the excretion of water, would consequently be limited to that one-eighth of the total nephron population whose loops of Henle traverse the medulla. Such selectivity is certainly possible; physiologic vagaries far more bizarre abound in nature. Nonetheless, this unitary hypothesis, which delegates to the antidiuretic hormone the function of stimulating the transfer of sodium and of water solely from the thin segment of the loop of Henle, in the interest of parsimony and uniformity of physiologic function, is offered as "enticing speculation."

Urinary Dilution.—Dilution of the urine, according to this hypothesis, results not so much because of the failure of the loops to establish a concentration gradient, as Wirz postulates,[62] but rather because the volume and rate of flow within the loops of Henle, and consequently within the more distal nephric structures as well, remains large in the absence of ADH relative to their values during antidiuresis. As has been pointed out, some degree of osmotic strati-

fication undoubtedly obtains within the long axis of Henle's loop even in the absence of ADH; however, under these circumstances, water and salt efflux from the thin limb is probably minimal, and the efficiency of the multiplier action is therefore quite limited, so that papillary osmolality rarely exceeds values of 300-450 mOsm. per liter. Rapidity of flow within the structures traversing the medulla minimizes the transmural diffusion of water down even this small gradient. Continuous removal of sodium salts from the distal tubule and collecting ducts accomplishes urinary dilution. Such kinetic considerations grant some logic to the fact that, in the absence of osmotic diuresis or other manipulation, minimal concentration is associated with a maximal rate of urine flow, and, conversely, maximum osmolality obtains only at minimal rates of flow.

Conclusion

It is disconcertingly all too apparent that much of present-day hypothesizing about the mechanism(s) ultimately responsible for dilution and concentration of the urine is largely conjectural; fabrication has been out of cloth generously perforated by large gaps in knowledge. The secrets of the characteristics of the tubular membranes and their metabolic activities remain largely to be discovered. Certainly experiments of a kinetic nature, by means of a model more closely akin to the kidney than that originally used by Hargitay and Kuhn[65] "would help decide whether the stratification of osmotic pressure within the kidney is the means whereby the urine is concentrated, or merely a consequence of prolonged concentration by other means."[90] What does emerge from the mass of data presently at hand is that (1) the hairpin configuration of the blood vessels and loops of Henle is not an anatomical quirk but implies specific functional significance with respect to the excretion of water and (2) osmotic stratification within the renal medulla seems to be definitely established. In order that homeoosmosis within the organism as whole be maintained, poikilosmosis, generally regarded as a primitive mechanism for the maintenance of volume homeostasis, utilized by the lowest forms of aquatic life, is also present in the renal medulla of the most highly developed mammals. If this be atavism, we, as befits our evolutionary status, seem to be making the most of it.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

A Bibliography of Internal Medicine, Communicable Diseases. By Arthur L. Bloomfield, M.D. Price, $10.00. Pp. 560, with no illustrations. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1958.

Continuity of medical thought, the history of the development of ideas, knowledge of the people who at various times in medical history have worked out complex problems—these elements of medical culture have fallen into such disrepair among the new generation of young physicians that the majority of them are as illiterate in this field as in the more esoteric aspects of the Sanskrit grammar. This puts them at risk of being mere technicians, the people who corral the chits from the laboratory, hoping to thumb through them and come out with a "diagnosis" so that they can apply "specific treatment" according to the cookbook. At the other extreme, we have medical scholars and teachers, those who have practiced medicine and adorned it with the impact of their presence, their personality, and their scholarship, as we see it in their teaching and writing. In this group, Arthur L. Bloomfield stands as a remarkable exemplar of medical excellence, a leader in a diminishing company of scholars. The publication in book form of his many masterful bibliographical critiques of various communicable diseases should be welcomed by student and practitioner, investigator and specialist. The book in its numerous sections provides not only basic facts about the major infectious diseases but what might be called the natural history of our knowledge of them or at least knowledge clarified through the work of two centuries of medical practice and investigation.

Not only is this a marvelous source book and reference book which puts one on the trail of many exciting adventures in the evolution of modern medicine, but it has the unique quality of having captured and saved for the use of others the accumulated wisdom of a wise medical scholar and teacher. Society has always been the loser when men of great experience, with wisdom enough for synthesis as well as analysis, leave the arena of active life. The great tragedy has always been that true learning and scholarship are not in the ordinary sense transferable. All too often they die completely with their owner. Here, however, much of the quintessential juice of scholarship has been distilled into a book which is at once a pleasure to read and a valuable incentive to the student who wishes to pursue knowledge back to its roots. Works such as this would not be possible without access to a great library, and the marvelous resources of the Lane Library of Stanford Medical School provided just the ideal working context for the scholarly pursuit of a bibliographer who is also a bibliophile.

To keep praise tempered with criticism, I give a little sigh that Daniel Drake's interesting observations about influenza, and his shrewd near misses in analysis of the cause of malaria and yellow fever, have escaped Dr. Bloomfield's all-seeing eye. But such a small fleck merely emphasizes the great perfection of the whole. It is a pleasure to say that this is one of the rare books published nowadays which establishes itself instantly as a medical classic. Every page reveals the painstaking care of the translator, the annotator, and the selector, but beyond this the great erudition is charmingly disguised so that it never becomes obtrusive. Any physician who wishes to *think* about diseases rather than just be vaguely aware of them must have this book.

WILLIAM B. BEAN, M.D.

Genetic Concept for the Origin of Cancer. By Leonell C. Strong, Ph.D. Price, not given. Pp. 432. New York Academy of Sciences, 2 E. 63d St., New York 21, 1958.

This monograph is the result of a series of papers presented at a conference on "Genetic Concept for the Origin of Cancer" in New York, Oct. 25 and 26, 1957. The monograph was prepared under the consulting editorship of Leonell C. Strong, Ph.D., with the joint sponsorship of the New York Academy of Sciences and the National Advisory Cancer Council, National Institutes of Health, United States Public Health Service.

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

Twenty-eight manuscripts were assembled ". . . (1) to review the historical development of the genetic concept for the origin of cancer, (2) to introduce new observations in the genetics of cancer, and (3) to give an opportunity to other scientists using different techniques to report their findings in order to ascertain whether these discoveries are complimentary or antagonistic to a genetic concept."

This monograph, making an effort to do these things, has gathered together many facets on the origin of cancer. Many and varied academic disciplines are included.

The monograph is paper bound.

ROBERT C. HICKEY, M.D.

Treatment of Breast Tumors. By Robert S. Pollack, M.D., F.A.C.S. Price, $6. Pp. 147, with 47 plates and 16 text figures. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1958.

Dr. Robert S. Pollack, aided by seven contributors, has directed his attention toward bringing together many loose ends in the diagnosis and treatment of breast cancer. The book is one of lucid conciseness in a cancer field with a voluminous literature. Of the twelve various chapters, Chapter 6, on "Breast Cancer," and Chapter 10, on "Treatment of Metastatic Breast Cancer by Oophorectomy, Hormones and Chemotherapy," are masterfully done. Favorable comment must be directed to Chapters 9 and 11, also.

It is meritorious that modified radical mastectomy is presented as a possibility for the poor-risk patient and also that the after-care of the mastectomy patient is emphasized.

I had some difficulties in transferring the "Pathologic Classification of Breast Tumors," Chapter 2, to the portion dealing with benign breast conditions, and later, in Chapter 7, to the histological grading of malignant lesions. In discussing cystosarcoma phyllodes, no clear attempt at clinical or histological differentiation is offered between the benign and malignant entities, yet the point is made that the therapy differs. These minor criticisms had to be searched for and are not particularly distracting, for I was pleased with the book and appreciate the advantages of brevity.

The text reflects foresight and planning by the author. The chapters have a pertinent bibliography directed to readily available journals and publications. The illustrations are plentiful and clear, and the print is very acceptable. The book is well bound. This book is recommended as up-to-date for the general surgeon dealing with cancer; it should be a welcome addition to every hospital library, particularly those with resident doctors.

ROBERT C. HICKEY, M.D.

The Malabsorption Syndrome. By David Adlersberg, M.D. Price, $5.50. Pp. 252, with many illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

Now that the alimentary canal has become accepted as a proper object for clinical research, we stand at the threshold of new discoveries and new concepts, but enough information has not yet accrued to let us know whether the malabsorption syndrome, so-called, is an entity, an inborn error of structure and of function of the alimentary canal which leads to a bewildering array of secondary deficiencies or whether a nutritional deficiency actually is an essential precursor or trigger mechanism which has to be sprung in order to bring the clinical discorder into an active and recognizable stage.

Despite the great amount of work which has been done on absorption in man and animals, many basic problems are far from solved, and it is against this background that Adlersberg and his colleagues have brought together this symposium. One shortcoming of the book is the lack of a detailed historical review, though the highlights, particularly of the recent past, are collected in considerable detail. The number of excellent illustrations add to the usefulness of the book, as do the tables, numerous case reports, and descriptions of original observations. The index is far too brief to be of much value and thus what should be an excellent reference book loses some of this function. Despite this limitation, however, within the covers of this volume are collected the essentials of present-day knowledge of the malabsorption syndrome or syndromes. They are presented in a way in which the information is accessible and may be used readily. This book is essentially for gastroenterologists and nutritionists and should help the internist and general physician.

WILLIAM B. BEAN, M.D.

Electrolyte Changes in Surgery. By Kathleen E. Roberts, M.D.; Parker Vanamee, M.D., and J. William Poppell, M.D. Price, not given. Pp. 113, with 21 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., and Blackwell Scientific Publications, 24-25 Broad St., Oxford, England, 1958.

There are books that are so disorganized and full of obvious untruths that one can immediately put them aside. There are others that are tantalizingly good but contain enough poorly expressed ideas and confusing paragraphs to give the reader a sense of insecurity over the parts he does not feel qualified to judge, with the result that the reader may discard the good along with the bad. There are books which are scholarly, with attention paid to the careful development of ideas and sufficient pertinent evidence for support of those ideas as to encourage the reader to consider the possible validity of even those ideas which seem foreign to his experience. The present book falls in the last category, probably by virtue of the fact that it is the culmination of a series of personal investigations by the authors into the subjects under discussion. Some of the pertinent bibliography can be found in subtitles of illustrations, but the text is without references. There is ample food for thought, which is not spoon-fed but which seems to be quite digestible if well chewed. According to the title, the book is written for surgeons but would be helpful to internists who, like the authors, are in the habit of working in close liaison with surgeons, physiological chemists, and surgical patients. Space is devoted primarily to problems of interest to the authors but at the same time to the more difficult problems that require detailed attention.

Fifty per cent of the book is devoted to alterations of acid-base balance and almost half of this to respiratory alkalosis. Hepatic failure takes up seventeen per cent and renal disease ten per cent of the book. The first topic is one that has received little if any treatment in most books on this subject and that is the potentially hazardous effect that preoperative bowel preparation may have on fluid and electrolyte balance and the need for recognition and treatment of this abnormality before surgery. Discussions of the possibility of inadequate blood volume preoperatively and excess fluid postoperatively and a section on complications of removing gastric and intestinal segments are the most surgical parts of the book.

Renal control of acid-base balance is discussed as a function of renal bicarbonate production and transport. Acid-base balance is discussed using total carbon dioxide of plasma and pCO_2 as parameters, adding welcome perspective to a subject which in most texts has become somewhat repetitious. There is an appendix which provides a little "unbiased philosophy" to soothe those readers who might have been looking for strict rules, it calls attention to the most common electrolyte abnormality encountered, "laboratory error." A table is provided for calculation of plasma pCO_2 and bicarbonate from the measured values of whole blood pH and total plasma CO_2. For those who wish to fill in between the select topics discussed, a list of thirty-six general references (texts and monographs) is provided.

EDWARD E. MASON, M.D.

A History of the Department of Internal Medicine, State University of Iowa, College of Medicine, 1870-1958. By Walter L. Bierring, M.D. Price, $3.50. Pp. 116, with many illustrations. State University of Iowa, Iowa City, 1958.

This book, which can comfortably be read through in an hour, will reward the reader with a quick and authoritative glimpse of the unfolding of medicine in the Midwest during the last century. While the focus is on Iowa City, the story of the efforts of a succession of dedicated doctors working diligently to bring good medicine to the heartland of America, has counterparts in Minneapolis, Madison, Chicago, St. Louis, and the other medical centers of the region. In a day when the start of any ambitious medical venture—be it research, teaching, disease prevention, or whatever—*begins* with a consideration of the dollars, tools, and space required it is heartening to recall that our forebears began their enterprises, with the gathering together of ". . . able men, some of great learning and even genius." The distinguished medical school now fluorishing in Iowa City had its beginning in Davenport, Iowa, in 1849, when a handful of earnest doctors pooled their intellectual and professional resources to begin to teach a class of eight students how to practice medicine. The financial resources were practically nil. Within a year the school moved to Keokuk and soon after became a department of the State University of Iowa.

Dr. Bierring's story really begins with the opening of the medical school in Iowa City, in 1870. All of the events chronicled occurred in his lifetime and in a major share of them he was an active participant. He received his M.D. from Iowa in 1892, became professor of

pathology and bacteriology the following year, and was chairman of the Department of Theory and Practice of Medicine from 1903 to 1910. Even after he relinquished this post to accept a similar position at Drake University, his interest in Iowa College of Medicine never flagged. It is natural and fitting that Dr. William Bean, present chairman of the Department of Internal Medicine at State University of Iowa, sought him out and finally induced him to undertake the history of the department.

There have been eight heads of the department during the years 1870-1958. The important events of the terms of each and the manner in which each shaped the institution are told with sympathy, brevity, and forthrightness. Dr. Bierring has a keen appreciation of the unique contribution that each of his predecessors, contemporaries, and successors was able to make, and one has the feeling that he genuinely admired and respected all of them. Characteristically the account of his own regime is devoted chiefly to a warm appraisal of his colleagues in and out of the department and to the development of many new features of the school. The unembellished recital of his own training in postgraduate centers here and abroad and of the hosts of important appointments and responsibilities he has had since fills one with wonder at his industry and fortitude.

The modern internist, fuming with frustration at the multiplicity of his tasks, will find himself chastened by a look at the undertakings of these hardy men who made Iowa medical history. For instance, Dr. Lawrence W. Littig, chairman from 1891 to 1903, owing to a restricted budget had no assistants. In addition to his administrative duties he conducted all the clinics, lectures, and recitations required in the curriculum, namely, a course in physical diagnosis for the sophomores and four lectures and one recitation each week for the seniors! Dr. William D. Middleton, who preceded Dr. Littig began his career as Professor of Physiology and Microscopic Anatomy, followed this with fourteen years as Professor of Medicine, then became Professor of Surgery!

The great European teachers of medicine, such as Lister and Gowers, of London; Roux, Metchnikoff, and Calmette, of Paris; Koch and Virchow, in Berlin, and Billroth and Nothnagel, in Vienna, were having tremendous influence on American medicine of the late nineteenth and early twentieth centuries. Their teachings were brought to Iowa chiefly by Littig and Bierring. Through his protege, Dr. Campbell P. Howard, Osler's teaching and example also had important impact on this middle western school. In the person of Dr. Fred M. Smith, Howard's successor, the influence of Herrick and Billings was brought from Rush Medical College to Iowa City. It was at this time that rapid expansion of the faculty and far-reaching changes in curriculum and organization took place. A major upheaval in the school administration took place in 1927-1928, resulting in many resignations, including those of key men from the department of medicine. The details of this and other minor storms which ruffled the calm at Iowa properly are omitted by the author, but their brief mention again serves to remind the reader that in the history of this school he is sampling the development of medical education throughout the nation.

The contemporaries of Dr. William Fowler, department head 1946-1948, and Dr. William Bean, present incumbent, will agree with Dr. Bierring that affairs at Iowa are still in good hands. When one compares the present faculty with the ones of early years of Iowa College of Medicine as to numbers, specialization, research output, and organization, he is deeply impressed with the tremendous growth of medicine in the last century and filled with admiration for this distinguished group of internists who have carried the torch so ably at Iowa City.

PAUL S. RHOADS, M.D.

The Management of Emergencies in Thoracic Surgery. By John Borrie, M.B.E., Ch.M., F.R.C.S. (Eng.), F.R.A.C.S. Price, $10. Pp. 340. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1958.

This book, even though it deals primarily with emergencies occurring in diseases of the chest wall and intrathoracic organs, also discusses some of the basic principles of the endobronchial anatomy and thoracic physiology as far as it is important to the clinician and thoracic surgeon. It also deals with the routine daily tasks of pre- and postoperative care, which should be of great help to residents in surgery facing those problems nearly every day. Some parts of the the book are practically an outline, listing the main points with only a little discussion. The way the subject matter is presented it forms a guide book for medical students, nurses, physical therapists, and other ancillary specialties. The book is also of value for orientation for residents in training in general and thoracic surgery. Several points in the treatment of thoracic

emergencies express the author's opinion rather forcefully. His statements are always well documented with case illustrations and a well-chosen bibliography.

The copy of the book submitted for review contains several gross errors in editing. Chapter 12 was inserted twice, and some of the schematic illustrations are mislabeled. The book is profusely illustrated, documenting various emergencies and certain surgical techniques with drawings and roentgenograms. The reproduction of some of the roentgenograms is only fair.

The main value of this book in my opinion is that the practical side of thoracic surgical practice is emphasized and presented in a precise, clear-cut, and lucid manner.

J. L. EHRENHAFT, M.D.

News and Comment

ANNOUNCEMENTS

Motion Picture on Cross Infections in Hospitals.—A 30-minute motion picture dealing with the over-all worldwide problem of cross infections in hospitals will be produced cooperatively by the American Medical Association, the American College of Surgeons, and the American Hospital Association. This timely and basically important film has been made possible by the cooperation and support of Johnson & Johnson of New Brunswick, N. J.

The film, which will be in sound and color, is designed to educate all levels of hospital personnel concerning the many avenues by which infection can be spread throughout a hospital and will utilize the Staphylococcus by way of illustration and as an example of one of the most important phases of the problem.

Produced under the supervision of Dr. Carl Walter, of Boston, Associate Clinical Professor of Surgery, Harvard Medical School, one of the recognized pioneer investigators in this field, and a committee representing the AMA, ACS, and AHA, it will deal with the broad fundamentals of phases of the problem and lay the groundwork for the delineation of the problems relating to specific fields in a series of shorter films to follow.

The presentation will have its premiere showing at the annual meeting of the American Medical Association in Atlantic City next June, again at the conclave of the ACS in October, and subsequently at professional gatherings throughout the world.

The production of this film will be coordinated by Ralph P. Creer, Chicago, Director of Motion Pictures and Medical Television of the American Medical Association.

Meeting of Congress on Occupational Health.—The 13th International Congress on Occupational Health—first to be held in the Western Hemisphere—will meet in New York, July 25 to 29, 1960, as announced by Dr. Leo Wade, of New York, chairman of the Organizing Committee.

All previous meetings have been held in Europe, beginning with the first one, in Milan, in 1906. The 12th Congress was in Helsinki, in 1957.

The Scientific Program Committee invites submission of papers for presentation at the Congress. The program will be devoted to the discussion of the following aspects of Occupational Health: (1) administrative practices, (2) medical practices, (3) surgical practices, (4) education and training, (5) social and legal aspects, (6) environmental hygiene, (7) influence of environmental factors in health, (8) work physiology and psychology, (9) specific industries, and (10) general.

The official languages of the Congress will be English, French, German, and Spanish. However, papers may be read at the Congress in the language desired by the author.

Henry G. Rudner Sr. Award Contest.—The American College of Gastroenterology takes pleasure in announcing the establishment of an award contest for the best unpublished paper on research in gastroenterology or an allied field. This award is to be known as the Henry G. Rudner Sr. Award, honoring Dr. Henry G. Rudner Sr., of Memphis, chairman of the Research Committee of the American College of Gastroenterology and former chairman of the Board of Governors of the organization.

This contest will be open to all those possessing the degree of Doctor of Medicine from a recognized medical school or university.

All papers submitted must represent original work in gastroenterology or an allied field and must not have been previously published except for abstracts or short preliminary reports. It must not have been previously presented on the program of any scientific meeting.

The contents of the papers can be clinical or basic science. Clinical papers must not be case records but controlled clinical work.

The length of a paper is no criterion for originality or value.

All entries for the 1959 award must be typewritten in English, double-spaced on one side of the paper, and submitted in six copies.

The winning entry will be selected by the Research Committee of the American College of Gastroenterology, and the award will be made at the annual convention banquet of the College, to be held in Los Angeles, in September, 1959.

The prize will be an award of $750 plus an additional $250 for traveling expenses to present the paper at the 24th annual convention of the College.

The paper selected for an award becomes the property of the American College of Gastroenterology, and the decision of the judges will be final. Should none of the papers submitted meet the standards set by the committee, the College reserves the right to withhold the making of any award.

All unpublished entries must be received no later than June 1, 1959, and should be addressed to The Research Committee, American College of Gastroenterology, 33 W. 60th St., New York 23.

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What differentiates "renal diabetes" (renal glycosuria) from diabetes mellitus?

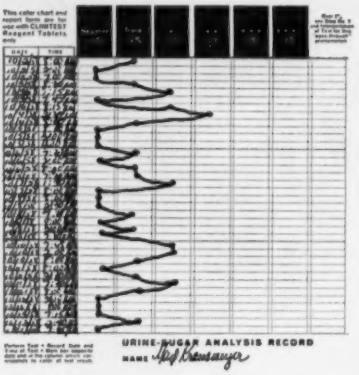
Blood sugar levels. In renal glycosuria they are normal; in untreated diabetes, fasting blood sugars are usually 130 mg.% or over and postprandial levels 170 mg.%, or more.

Source: Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, pp. 701-702.

A "URINE-SUGAR PROFILE" FOR CLOSER CONTROL

The new CLINITEST Urine-Sugar Analysis Set contains an improved Analysis Record form that enables even closer control of the *moderate* and the *severe* diabetic. Daily urine-sugar readings may be connected to produce a graph—a day-to-day "profile" that reveals at a glance individual trends and degree of control.

*GP *16*:121 (August) 1957.



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In clinical trials with some 1,500 patients glycosuria was noted in only two, transitory glycosuria in another two, and flattening of the glucose tolerance curve in one. There were no instances of aggravation of existing diabetes, no increase in insulin requirements. Patients whose diabetes was severely aggravated on prednisolone showed good tolerance when transferred to DECADRON.

MORE patients can be treated with DECADRON than with other corticosteroids, because in addition to being practically free of diabetogenic activity, therapy with DECADRON is also practically free of sodium retention, potassium depletion, hypertension, edema and psychic disturbances. Cushingoid effects are fewer and milder. DECADRON has not caused any new or "peculiar" reactions, and has produced neither euphoria nor depression, but helps restore a "natural" sense of well-being.

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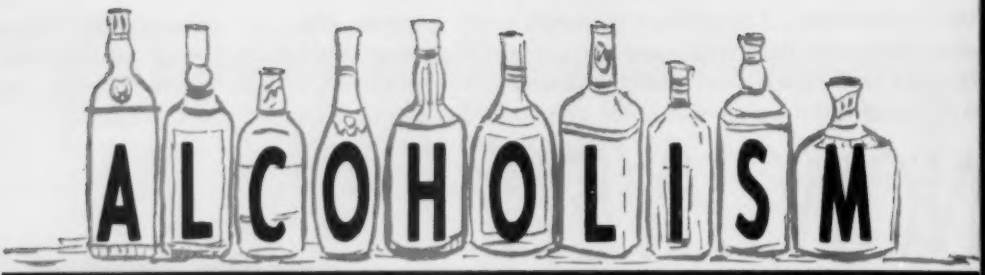

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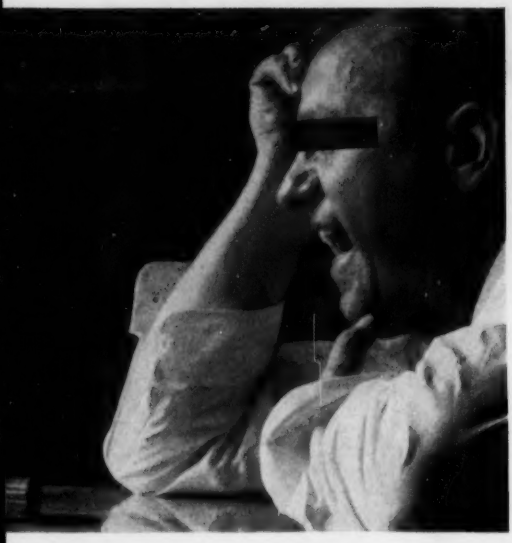

in alcoholism[1, 2]

ACUTE EMERGENCIES—a single intramuscular injection of 50 mg. (2 cc.) Vistaril Parenteral Solution is usually sufficient to calm the patient and initiate sound sleep. Vistaril is exceptionally well tolerated. Antiemetic action and absence of respiratory depression are among valuable assets reported.

REHABILITATION—oral administration of 100-400 mg. daily in divided doses provides psychotherapeutic action which maintains calm and confidence, and promotes anxiety-free abstinence. The remarkable safety of Vistaril is reassuring in long-term maintenance.

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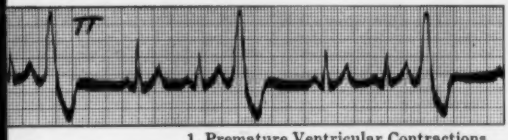
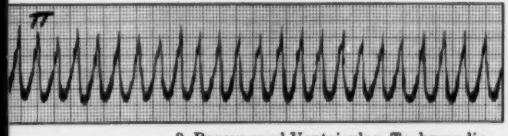


1. Premature Ventricular Contractions

2. Paroxysmal Auricular Tachycardia



3. Paroxysmal Ventricular Tachycardia

in arrhythmias[3, 4]

Many types of cardiac arrhythmias respond promptly to oral, intramuscular or intravenous Vistaril therapy. Vistaril is particularly effective in ventricular extrasystoles, paroxysmal tachycardias (both auricular and ventricular), and ventricular extrasystoles complicating auricular fibrillation. The following dosage regimen is recommended:

PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h. p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

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ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY:
Vistaril Capsules, 25 mg., 50 mg. and 100 mg.
Vistaril Parenteral Solution, 10 cc. vials, and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydrozyzine hydrochloride.

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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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Esidrix™

(hydrochlorothiazide CIBA)

milligram-for-milligram,
the most active oral
diuretic-antihypertensive

New diuretic-antihypertensive with high degree of activity, low toxicity

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Minimum dietary salt restriction: In many cases, Esidrix permits some moderation in severe sodium restriction and therefore makes meals more palatable. Side effects are usually not severe and most of them can be overcome by adjusting the electrolyte balance (through dietary supplements), lowering the dose or administering the drug after meals.

Dosage: Esidrix is administered orally in an average dose of 75 to 100 mg. daily, with a range of 25 to 200 mg. A single dose may be given in the morning or tablets may be administered 2 or 3 times a day.

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Following periods of catabolic stress—when rehabilitation by diet is especially important—many patients cannot tolerate certain high-nutrition foods, and frequently show an aversion to foods with high-fat content.

Under such circumstances the physician is faced with the problem of selecting nourishing foods which are easily digested and well tolerated. Each day's menu must be built from a variety of high-protein, high-nutrient foods which appeal even to jaded appetites.

Oatmeal is an outstanding source of natural nutrients well suited for debilitated patients. It ranks highest among whole-grain cereals in content of protein, thiamine, and phosphorus.

The oatmeal serving with milk provides high-quality protein, unimpaired in processing or preparation. It supplies the essential amino acids in proper proportions for biosynthesis, repair, and replenishment of tissue. Oatmeal also provides significant amounts of several B vitamins and minerals important to physiologic rehabilitation.

The smooth, semi-solid texture of oatmeal, the ease of its digestibility, its inviting warmth, and its delicious nut-like taste combine to make it an appealing dish to patients of all ages.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

IN DIETARY MANAGEMENT, virtually regardless of the adjustment to be made, oatmeal proves remarkably valuable. It is low in sodium, low in purines, low in inert residue, high in protein, notable for its vitamin and mineral content, yet not excessive in calories.

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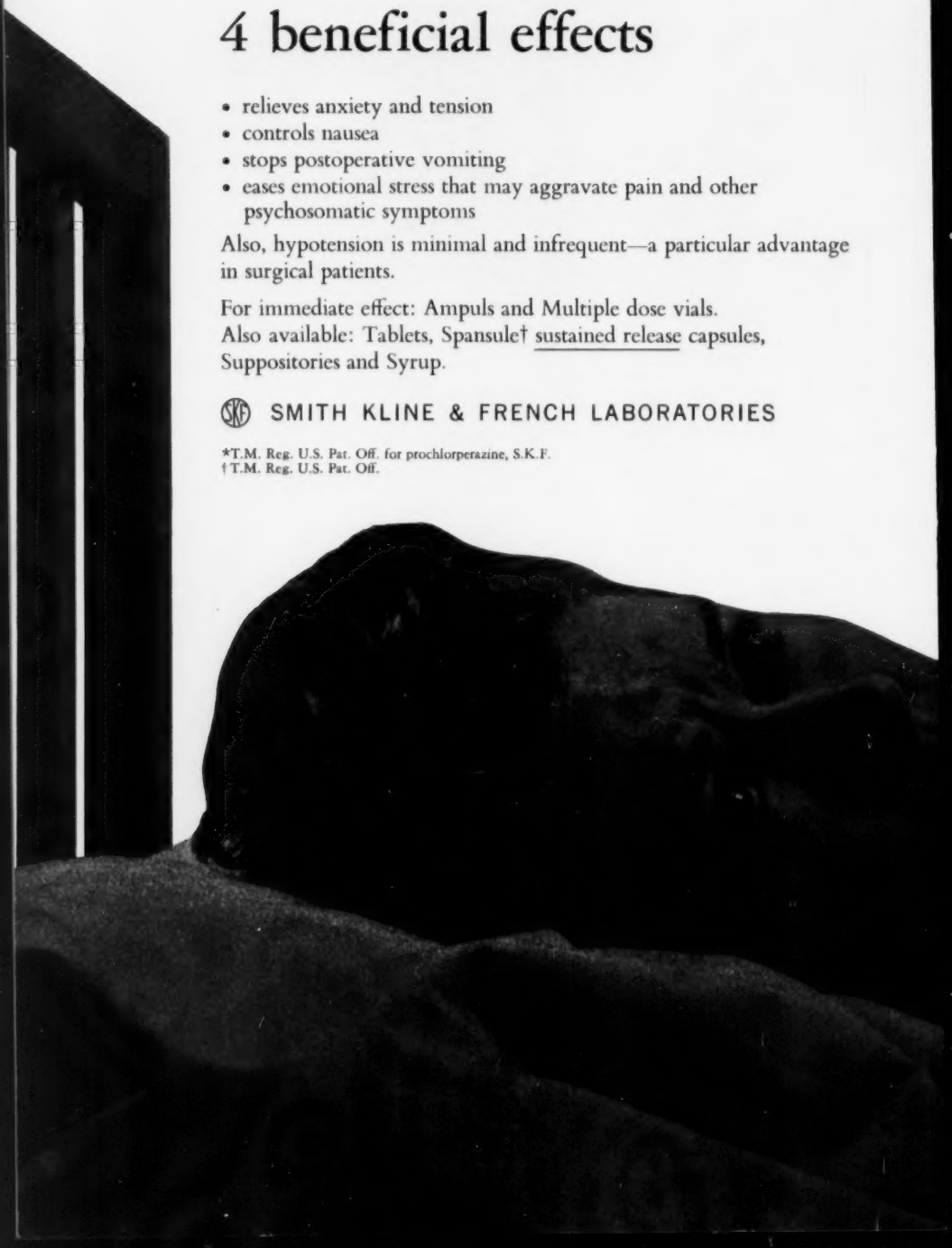
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